No cry at birth

Neonatal resuscitation in low-resource settings: role of the laryngeal mask airway

Nicolas J Pejovic

Thesis for the degree of Philosophiae Doctor (PhD)
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No cry at birth. A silent crisis. We are less willing to tolerate the millions of unnecessary newborn deaths, but the fact is that we still have unfinished business. I dedicate this thesis to all of you that fight in the trenches, making it a better world for mothers and babies.

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Scientific environment

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Abbreviations and definitions

AE	Adverse event
BA	Birth asphyxia
Bpm	Beats per minute
CISMAC	Centre for Intervention Science in Maternal and Child Health
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CI	Confidence interval
ECG	Electro-cardiogram
END	Early neonatal death
ENAP	Every Newborn Action Plan
ETT	Endotracheal Tube
FM	Face-mask
FMV	Face-mask ventilation
FRC	Functional residual capacity
GCP	Good Clinical Practice
GLM	Generalized linear model
HBB	Helping Babies Breathe
HIE	Hypoxic-ischemic encephalopathy
HR	Heart rate
IDMC	Independent Data Monitoring Committee
ILCOR	International Liaison Committee on Resuscitation
IQR	Interquartile range
ITT	Intention-to-treat Analysis
IVA	Instrumental Variable Analysis
LM	Laryngeal mask
LMA	Laryngeal Mask Airway
LMIC	Low and middle-income country
MAP	Mean airway pressure
MDGs	Millennium Development Goals
MREC	Mulago Research and Ethics Committee
NE	Neonatal Encephalopathy
NICU	Neonatal Intensive Care Unit
NLS	Newborn Life Support
NRP	Neonatal Resuscitation Program
LS	Life Support
NNT	Number of patients needed to treat (to prevent an outcome)
PBF	Pulmonary blood flow
PIP	Peak inspiratory pressure
PP	Per protocol analysis
PPV	Positive Pressure Ventilation
QA	Quality Assurance
RA	Research assistant
RCN	Research Council of Norway
RFM	Respiratory function monitor

RR	Relative risk
s	seconds
SAD	Supraglottic airway device
SO_2	Oxygen Saturation
SpO_2	Peripheral capillary oxygen saturation
SAE	Severe Adverse Event
SGA	Supraglottic Airway
SDGs	Sustainable Development Goals
SUSAR	Suspected Unexpected Serious Adverse Reaction
UN	United Nations
UNICEF	United Nations Children's Emergency Fund
Vte	Expired tidal volume
Vti	Inspiratory tidal volume
WHO	World Health Organization

Definitions

APGAR = backronym for Appearance, Pulse, Grimace, Activity and Respiration

Perinatal Mortality (WHO) = number of stillbirths and deaths in the first week of life per 1,000 births. The perinatal period commences at 28 completed weeks (196 days) of gestation, and ends 7 completed days after birth.

Neonatal Mortality = newborn deaths within the first 28 days of life per 1000 live births

Early Neonatal Mortality = newborn deaths within the first 7 days of life per 1000 live births

Birth asphyxia (WHO) = failure to establish respiration at birth

MR SOPA: acronym for **M**ask **R**eposition, **S**uction, **O**pen mouth, increase ventilation **P**ressure, **A**lternative airway

Primary apnea = heart rate considered to be > 60 beats/min with compensated blood pressure

Secondary apnea = progressive bradycardia < 60 beats/min and hypotension with final gasping

Gestational age = defined as the best estimate of the newborn's gestation in completed weeks based on the final estimate of gestation, irrespective of whether the gestation results in a live birth or a fetal death.

Abstract

Background: Approximately 2.5 million newborn infants died in the first month of life in 2019, despite the global rate being halved since 1990. The current newborn mortality rate in Sub-Saharan Africa is > 20 times higher than the average ratio of 1 in 600 found in high-resource countries. Intrapartum-related death or birth asphyxia is the third leading cause of under-5 mortality and contributes significantly to global long-term developmental disability. Effective ventilation has the potential to reduce 30% of these deaths. The laryngeal mask airway (LMA) is an airway tube that can be blindly inserted through the mouth of a non-breathing infant to form an airtight seal around the glottis. This device could improve neonatal resuscitation.

Aim: To investigate whether midwives in low-resource settings could safely resuscitate newborns more effectively using LMA instead of a conventional face-mask (FM).

Methods: We conducted a preclinical manikin study and 2 randomized clinical trials in Uganda. Health workers involved in neonatal resuscitation were given brief training with LMA and FM. We recorded success rate and insertion times, leading to effective ventilation in the manikin. Participants rated the perceived efficiency of the devices using a 5-point scale. In the 2 clinical trials, midwives performing resuscitation after delivery of asphyxiated newborn infants were randomly assigned to ventilate with either LMA or FM. In the first trial, we collected data on ventilation time with a video monitor and heart rate (HR) with the NeoTap LS mHealth App. In the second trial, respiratory function was measured through a flow sensor, and HR data collected with a dry-electrode ECG.

Results: In the preclinical trial, LMA was 100% successful on the first insertion. FM was significantly less effective in achieving effective positive pressure ventilation (PPV), and the failure rate at the first attempts was 28%. The perceived efficiency of the devices was superior for the LMA. In the first clinical trial, resuscitated infants started breathing on their own sooner in the LMA arm compared to FM. All resuscitations were effective in the LMA arm, and there were no side effects. In the second trial, mask leak (%) and tidal volume (ml/kg) were similar in both groups. The time needed to achieve heart rate >100 bpm in LMA was shorter than in the FM arm. There were no severe adverse events in either arm.

Conclusion: LMA was more effective in establishing PPV in the manikin and user satisfaction was higher. LMA was more effective than FM in reducing the time to spontaneous breathing. LMA was associated with faster heart rate recovery compared to FM in newborns with bradycardia. Mask leaks and tidal volumes using LMA was similar to FMV. LMA seems to be a safe and effective device for newborn resuscitation in low-resource settings.

List of publications

Paper I:
Pejovic NJ, Trevisanuto D, Nankunda J, Tylleskär T.
Pilot manikin study showed that a supraglottic airway device improved simulated neonatal ventilation in a low-resource setting
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Paper II:
Pejovic NJ, Trevisanuto D, Lubulwa C, Myrnerts Höök S, Cavallin F, Byamugisha J, Nankunda J, Tylleskär T.
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Arch Dis Child. 2018 Mar;103(3):255-260. doi: 10.1136/archdischild-2017-312934.

Paper III:
Pejovic NJ, Cavallin F, Mpamize A, Lubulwa C, Myrnerts Höök S, Byamugisha J, Nankunda J, Tylleskär T, Trevisanuto D
Respiratory monitoring during newborn resuscitation using a laryngeal mask airway vs. a facial mask: a quasi-randomized trial
(submitted manuscript)

Annex:
Pejovic NJ, Myrnerts Höök S, Byamugisha J, Alfvén J, Lubulwa C, Cavallin F, Nankunda J, Ersdal H, Segafredo G, Blennow M, Trevisanuto D, Tylleskär T
Neonatal resuscitation using a supraglottic airway device for improved mortality and morbidity outcomes in a low-income country: study protocol for a randomized trial.
Trials. 2019 Jul 19;20(1):444. doi: 10.1186/s13063-019-3455-8.

Thesis at a glance (paper I-III + annex)

Participants	Health workers performing newborn resuscitation (paper I) and infants in need of PPV with gestational age >34 and birth weight >2000 g (paper II-III, Annex)
Paper I	25 participants
Aim	To compared the performance of personnel in in Uganda when using an LMA or a FM on a manikin
Methods	25 health workers involved in neonatal resuscitation were given brief training with LMA and FM. Success rate and insertion times leading to effective PPV were recorded. Participants rated the perceived efficiency of the devices using a five-point scale.
Results	LMA achieved a 100% success rate on first insertion. FM was significantly less effective in achieving effective PPV and the failure rates at the first attempts were 28%. The perceived efficiency of the devices was significantly superior for the LMA.
Conclusions	LMA was more effective than FM in establishing PPV in the manikin, and user satisfaction was higher.
Paper II	49 participants (24 LMA, 25 FM)
Aim	To compare LMA to FM during neonatal resuscitation in a low-resource setting.
Methods	Prospective randomised clinical pilot trial conducted at the labor ward operating theatre in Uganda. After a brief training on LMA and FM use, infants with a birth weight >2000 g and requiring positive pressure ventilation at birth were randomised to resuscitation by LMA or FM. Resuscitations were video recorded. The primary outcome was time to spontaneous breathing. The secondary outcomes included conversion to other device and side effects.
Results	Time to spontaneous breathing was shorter in LMA arm than in FM arm. All resuscitations were effective in LMA arm, whereas 11 patients receiving FM were converted to LMA because response to FMV was unsatisfactory. There were no adverse effects.
Conclusions	LMA was more effective than FM in reducing time to spontaneous breathing. LMA seems to be safe and effective in clinical practice after a short training program.
Paper III	46 participants (26 LMA, 26 FM)
Aim	To evaluate the respiratory function of an i-gel laryngeal mask airway (LMA) vs. a face mask (FM) in asphyxiated newborns resuscitated by midwives in a low-resource setting
Methods	This quasi-randomized trial evaluated respiratory monitoring during newborn resuscitation in Uganda. Same inclusion criteria as paper II. The primary outcome was difference in mask leak (%). The secondary outcomes included inspired (Vti) and expired (Vte) tidal volumes, and change in heart rate (HR).
Results	Mask leak was 39% in the LMA and 46% in the FM arms (p=0.32). Shorter time was needed to achieve heart rate >100 bpm in LMA with respect to FM arm. Three newborns in FM arm and none in i-gel arm were converted to the alternative device.
Conclusions	Respiratory function was not different between LMA and FM in resuscitated newborns. LMA was associated with faster heart rate recovery compared to FM in newborns with bradycardia.
Annex	1164 participants (trial protocol)
Aim	To investigate whether the use of a cuffless supraglottic airway device compared with face-mask ventilation during neonatal resuscitation can reduce mortality and morbidity in asphyxiated neonates.
Methods	A randomized phase III open-label superiority controlled clinical trial will be conducted in Uganda. Infants with a birth weight >2000 g and in need of PPV at birth will be randomised to LMA or FM. The primary outcome will be a composite outcome of 7-day mortality and admission to neonatal intensive care unit (NICU) with neonatal encephalopathy

Contents

1. Introduction

Our societies need to commit to the health of newborn. Facility-based interventions focused on the perinatal period are crucial if we want to improve survival.[1 2] Life is most vulnerable when babies are not breathing at birth. Neonatal resuscitation is the art of saving those lives by acting quickly and efficiently.

We have set ambitious goals both for the survival of mothers and babies, but are we on track? Despite all efforts, reduction of neonatal mortality in parts of Asia and Sub-Saharan Africa, is occurring at only half the speed of maternal mortality or child mortality after the first month. Our efforts must also include a bold approach to innovations targeted at the most vulnerable populations. Developing, investigating, and implementing new technology for newborn health may help accelerate a reduction in neonatal mortality.[3]

1.1 Neonatal mortality

In 2015, after summarizing the Millennium Development Goal number 4 (MDG-4) of globally reducing by two-thirds the under-5 (years of age) mortality, it became evident that the neonatal mortality was not decreasing at the expected pace.[4] The third leading cause of child mortality for the under-5s is intrapartum-related death, commonly referred to as birth asphyxia (BA). An estimated 5% or ~7 million of the 140 million babies born in the world annually are not breathing at birth. Immediate resuscitation, including effective stimulation and ventilation, is necessary if these babies are to survive.

The Demographic and Health Survey indicators from Uganda in 2017 show that under-5 mortality had decreased from 175/1000 in 1990 to 53/1000 in 2016.[5] Estimates indicate that 27/1000 newborn infants will not survive the first month. The situation has remained unchanged in Uganda (table 2) over this last decade despite the national roll-out of Helping Babies Breathe (HBB),[5 6] a neonatal resuscitation training program for resource-limited settings.[7] HBB implementation trials have demonstrated a reduction in fresh stillbirths and first-day neonatal mortality.[8-10]

The Sustainable Development Goal number 3 (SDG-3) re-emphasizes the need for accelerating the reduction of neonatal mortality; each country should try to achieve a neonatal mortality of < 12/1000 live births by 2030. As of 2018, 78 of 195 countries are still not on track. We need to radically improve existing newborn resuscitation programs if we wish to achieve this goal.[11] Physicians, midwives, and other staff attending birth should have the knowledge and skills required to perform effective neonatal resuscitation.[12] We also need to strengthen existing strategies with innovative tools that can be rapidly implemented if we are to reach the 12/1000 target of neonatal death by 2030. The commitment to reduce global neonatal mortality under the Sustainable Development Goals was pronounced in 2015 by United Nations Children's Emergency Fund (UNICEF), Every Newborn Action Plan (ENAP), and the World Health Organization (WHO). ENAP has set up a particularly ambitious agenda to end all preventable newborn deaths by 2035.[11]

1.2 Disease burden

The latest estimates are that 717 000 deaths annually are caused by Birth Asphyxia (BA),[13] making it globally the third leading cause of under-5 mortality.[14] BA also contributes with 42 million disability-adjusted life years lost long-term to neurodevelopmental disability.[15] Sequelae in survivors include developmental delay, cerebral palsy, cognitive impairment, epilepsy, hearing impairment and behavioral problems. Interventions are likely to have a positive impact on morbidity. Carlo et al. suggests that infants born in resource-limited rural communities who survived after bag and mask resuscitation had an 82% chance of having normal mental development (MDI > 85%) and an 84% chance of being free of severe disability when one year old.[16] These are similar outcomes to non-resuscitated infants.

1.3 Surviving birth

Ersdal et al. have outlined a 3-phase prevention strategy[17] that could reduce intrapartum-related adverse outcome:

1) Primary prevention: Delivery of high-quality obstetric and antenatal care that impacts early hypoxic insults to the fetus. This strategy has the greatest life-saving potential, but relies on interventions in a complex health system.[15 18-20]
2) Secondary prevention: Babies born with hypoxic insults who receive effective care at birth can survive with a high rate of successful outcomes. Such interventions can be achieved within a short time frame also in low-resource settings.[9-11 21-27]
3) Tertiary prevention: Delivery of high-quality neonatal care can prevent further complications due to birth asphyxia, but are dependent on technologically advanced facility-based services requiring specialized staff.[28-30]

The time horizon and expenses involved in improving health systems in low- and middle-income countries (LMIC) make secondary prevention highly relevant. Even in technologically advanced settings, the currently accepted standard of having skilled personal ready to perform neonatal resuscitation at every birth, took decades to become a reality. This reality has not yet been achieved in resource-limited settings.[24]

The ENAP aims to reduce global neonatal death to < 10 per 1000 live births by 2035. The current rate is 2.3 per 1000 in Western Europe, 27 per 1000 live births in sub-Saharan Africa and 18 per 1000 as the world average. Each year, 170 000 intrapartum related deaths could be saved by the widespread implementation of newborn resuscitation.[31] National rollouts of HBB have emphasized the need to strengthen the knowledge and skills of birth attendants as well as teamwork.[32] Implementation of HBB has improved rates of stillbirth and first-day survival.[8 10 33] On-site, high frequency/low dose training has reduced 24-h mortality by 40%.[8] Better delivery room management could delay death by birth asphyxia, that typically occurs after 3-5 days. Studies reporting mortality through discharge or at 28 days show little change in overall mortality.[10 34] Further efforts will be needed to translate new knowledge and skills into sustainable clinical practice.

1.4 From liquid to air

Birth should be accompanied by the first breath and transition to independent life. Gas exchange in the newborn shifts from the placenta to the lungs soon after the umbilical cord is clamped and lung aeration must rapidly be achieved by clearance of any liquid-filled airways. Extra-uterine survival also involves major cardiovascular changes, redirecting much of the cardiac output towards the lungs.

Fetal lungs develop in a liquid-filled distended state, critical for normal extra-uterine function.[35] Breathing movements are initiated by the fetus at 11 weeks of gestation. Fetal respiration becomes more organized towards the end of pregnancy, reaching a rate of 30-70 /minute.[36] The majority of babies (93%) successfully transition at birth and start breathing within 30 seconds.[37] A switch of net secretion drives clearance of lung liquid to net absorption by an interaction of epinephrine, oxygen, glucocorticoids, and thyroid hormone in the distal lung epithelium.[38] However, lung aeration is also associated with inspiration through generation of hydrostatic pressure and occurs more rapidly than can be achieved by fluid reabsorption alone.[39 40] Typically newborns clear their airways within 2-5 breaths.[41] The pressure gradient generates a flow of lung liquid to tissues surrounding the alveoli, thereby increasing interstitial pressure.[39]

Increased aeration triggers the activity of vasodilating agents and various mechanical effects that increase pulmonary blood flow (PBF).[42] Left ventricular preload shifts from the umbilical venous return to pulmonary venous return. Systemic vascular resistance increases simultaneously to result in left-to-right flow through the ductus arteriosus, leading eventually to ductal closure.[43] Mean oxygen saturation (SO_2) in the fetus is 58%[44] and can decrease to 30% during labor.[45] Median peripheral oxygen saturation (SpO_2) after birth reaches 68% at 1 minute, 92% at 5 min and 97% at 10 min in term infants.[46] Median heart rate (HR) at birth is <100 and stabilizes around 160 after 3 min.[47 48] At this point, most of the lung fluid is cleared from the alveoli; ventilation and blood flow are finally harmonized.

1.5 Failing to breathe

The WHO defines BA as the clinical description of a newborn who "fails to initiate or maintain regular breathing at birth".[49] BA results of the impairments of gas exchange to the fetus or newborn during labor or directly after birth. Prenatal events, such as umbilical cord occlusion, placental dysfunction, uterine rupture, maternal hemodynamic compromise or infection, are the leading causes of perinatal asphyxia.[50 51] The most severe cases result in fresh stillbirth (FSB) or early neonatal death (END). Postpartum events are most often caused by impaired cardiovascular transition, respiratory pathologies such as meconium aspiration syndrome (MAS), and airway obstruction by viscous secretions.

The common underlying pathogenetic pathways of these events are *hypoxemia*, reduced oxygen pressure in the blood supply, and *ischemia*, reduced blood perfusion.[52] Glucose is the other major driving force in energy production in the brain. Under anaerobic conditions, the generation of high energy phosphate compounds from glucose is markedly reduced, but it also results in lactate accumulation. A further cascade of events, including intracellular acidosis, formation of free oxygen radicals, glutamate, and nitric oxide, finally lead to cell death. In survivors, this leads to hypoxic-ischemic encephalopathy (HIE). HIE must be differentiated from other causes of neonatal encephalopathy (NE) such as sepsis, meningitis and metabolic disorders.[53]

The initial response to BA is primary apnea (heart rate >60 beats/min and normal blood pressure) during which proper stimulation may result in the resumption of breathing (figure 1).[54-56] If intervention is delayed or the infant fails to respond, an infant will progress to secondary apnea (heart rate <60 beats/min with hypotension). Continued stimulation will not help, and positive pressure ventilation (PPV) is required. Primary and secondary apnea may clinically appear similar.

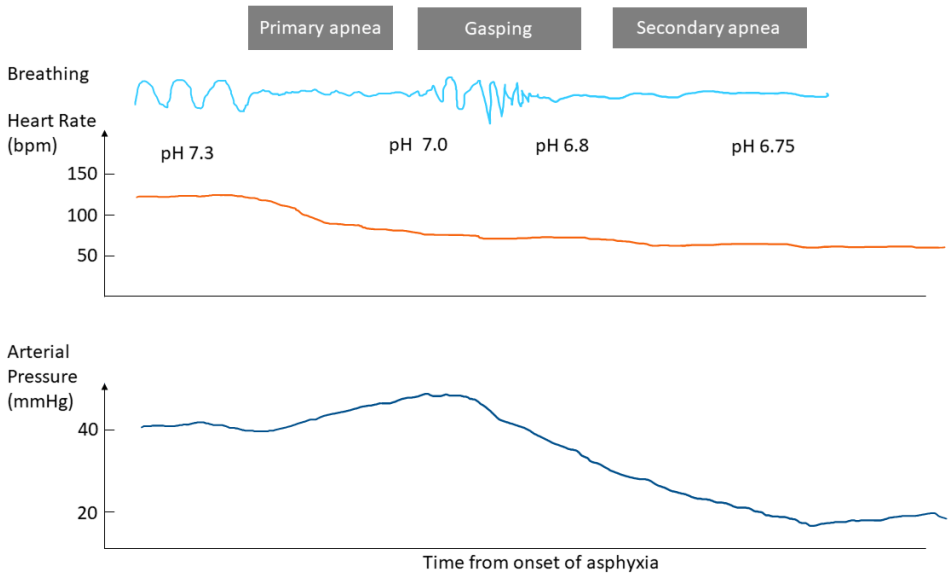

Figure 1. *Physiological changes associated with primary and secondary apnea in the newborn. (Adapted from Kattwinkel Neonatal Resuscitation Textbook, 5th Edition, 2006)*

Infants with profound bradycardia may be indistinguishable from fresh stillborn (FSB),[57] and failure to identify and resuscitate these infants often leads to a misclassification of FSB, influencing global perinatal mortality estimates.[58]

In 1952, Dr. Virginia Apgar introduced a scoring system that is a rapid method of assessing the clinical status of the newborn, providing a standardized assessment for infants after delivery and a mechanism to record fetal-to-neonatal transition.[59-63] The Apgar score has 5 components: color, heart rate, reflexes, muscle tone, and respiration. Birth attendants give a score of 0, 1, or 2 to each component. The Apgar score is an assessment tool that cannot explain the etiology of the asphyxia but can give relevant information on neonatal outcome.[64] The quality of the scoring can vary between observers.[65] On a population basis, Apgar scores < 5 at 5 and 10 min correlate with an increased risk of cerebral palsy. An Apgar score at 5 min of 7 or more is associated to a favorable neurological outcome.[60 66 67]

1.6 Back to life

And when Elisha came into the house, behold, the child was dead, and laid upon his bed... He went up, and lay upon the child, and put his mouth upon his mouth ... and the flesh of the child waxed warm... and the child sneezed seven times and opened his eyes.

Old Testament

The transition from a fluid-filled lung to an aerated lung of a breathing infant requires the establishment of functional residual capacity (FRC). The most effective practice remains controversial.[32] Since times immemorial, it has been accepted that "life ends when the respiration ceases." Different cultures have explored the importance of securing the airway with invasive devices since 4000 years ago.[68] In 1754, Benjamin Pugh resuscitated infants using mouth to mouth and a coiled wire and soft leather endotracheal tube.[69] In the mid-18th century, mouth-to-mouth resuscitation was recognized as effective,[70] but fell out of favor after William Hunters designed a popular bellow for inflating the lungs.[71] Immersion in a cold and hot water bath, and a variety of other harmful stimulation methods remained popular until the 1950s. Traditional birth attendants in rural Sub-Saharan Africa still blow air in the baby through a fetoscope - the instrument normally used for listening to fetal heart sounds - and mouth to mouth is practiced with WHO recommendations despite the risk of infection.[49 72] However, the self-inflating bag, invented in 1958, finally became the standard of choice.

In low-resource settings, face-mask ventilation must function without a source of oxygen or airflow. In 1998, WHO implemented the first practical guide for basic newborn resuscitation[49] after surveys had shown that many institutions, including central hospitals, lacked proper resuscitation equipment and trained health personnel. The commission identified both recent and traditional practices, either non-beneficial or harmful for the infant, and recommended evidence-based methods. Preventive measures were also emphasized, such as preparation for birth, cleaning of equipment, prevention of hypothermia, proper hygiene, and essential newborn care. The basic resuscitation skills that focused on prompt delivery of PPV using a self-inflating bag and mask with room air remain valid today.[73] In 2000, the International Liaison

Committee on Resuscitation (ILCOR) released the first consensus on science and treatment recommendations for neonatal resuscitation based on a systematic review of the quality of the evidence. The ILCOR consensus on neonatal resuscitation has been updated every 5 years and focuses mainly on resuscitation practices for resource-intensive settings.[12 74] The first guideline targeting resource-constrained settings was published by WHO in 2012. It still focused on the core principles of newborn management that have remained unchanged for many decades. HBB is the initiative of the American Academy of Pediatrics, the WHO and other collaborative partners to develop a comprehensive educational training program based on the ILCOR consensus on science with treatment recommendations.[7 75] HBB has been harmonized to the WHO guidelines and was updated to HBB second edition in 2018.[7] It has been implemented in more than 80 countries and is primarily targeted at midwives and auxiliary community-based birth attendants.[76] A network of master trainers has instructed 500 000 health providers and the curriculum has been translated into twenty-seven languages.[7] The HBB Action Plan emphasizes skills and team training. Non-crying babies should be stimulated and have their airways cleared by proper positioning and removal of secretions as necessary. Birth attendants should initiate PPV within 60 seconds, 'the Golden Minute'. Advanced interventions such as alternative airways, chest compressions, volume expansion and provision of oxygen are not part of the HBB training.[11] More research is needed to evaluate intermediate algorithms targeted at health facilities with mid-level providers or specialists found in urban facilities. The urban-rural gaps in facility birth are improving as a result of the 2030 agenda[77] and efforts should continue to develop hospital-specific neonatal emergency training programs.

1.7 Conventional respiratory devices

The UN established the Commission on Life-Saving Commodities in 2012. The commission's goal was to promote and increase access to 13 life-saving commodities that could alleviate preventable causes of death during pregnancy, birth, and childhood. The essential commodities for basic neonatal resuscitation include the self-inflating bag and mask and suction devices.[78]

1.7.1 The self-inflating bag

The self-inflating bag is the only device that can deliver PPV without an external source of air or oxygen; it is the favored system in low-resource settings. The typical bag size for neonates is 220-240 ml. The tidal volume required for term babies is 4-8 ml/kg or approximately 13-25 ml per delivered breath. The reserve in volume can offset leakages, but may also deliver excessive volumes, especially in preterm babies. The level of Peak Inspiratory Pressure (PIP) is operator-dependent, with increased squeezing to the bag providing higher pressure. Self-inflating bags of reasonable quality are relatively cheap at 12-20 $.[11]

Many self-inflating bags are single-use, but models such as the Laerdal Neonatalie provided with the HBB curriculum are reusable. Cleaning the devices, however, is costly and time-consuming, with improper routines leading to equipment failure.[79]

Figure 2. *Laerdal bag and two face-masks of different sizes. (With kind permission from Laerdal Global Health)*

1.7.2 Face-mask ventilation (FMV)

Resuscitation of infants using FMV (figure 2) is a well-accepted technique and "standard of care" in virtually all countries. The key features that will offer the best results are a round mask, with a soft rim that forms an adequate seal, and a reservoir

that delivers air.[80] In our studies, a high-end Laerdal reusable silicone resuscitator provided PPV because it has a robust design, is easy to clean, and includes an effective silicone mask (figure 2).[81]

Difficult mask ventilation occurs as a result of 2 primary mechanisms: an inadequate seal between the face and the mask, and upper airway collapse or obstruction.[68] The MR. SOPA mnemonic was introduced by the Neonatal Resuscitation Program (NRP) to address these problems. Mask reposition and adjustment (MR) can minimize leakage. The suction of the airways (S) with a bulb or catheter deals with obstruction due to secretions. Opening the mouth (O) decreases airflow resistance. High lung compliance due to lung fluid may necessitate an increase in peak inspiratory pressure (P). Should these measures fail, the final step is the placement of an alternative airway (A) such as an endotracheal tube (ETT) or a laryngeal mask airway (LMA).

1.7.3 Endotracheal tube (ETT)

In case of ventilation failure with FMV, resuscitation should be followed by intubation with ETT.[82] Placing an ETT is often challenging and requires a laryngoscope, and is usually fitted in the neonate by skilled anesthesiologists or neonatologists. There are several problems with endotracheal intubation that necessitate additional equipment on the resuscitation table, such as an active suctioning device. Cardiopulmonary failure may be secondary to perinatal asphyxia caused by improper tube placement.[83] ETT placement may also result in more side effects (laryngospasm, bronchospasm, glottic and subglottic trauma) than LMA in pediatric surgical procedures.[84] It is not considered a practical alternative airway for PPV in low-resource settings.

1.8 Laryngeal mask airway (LMA)

The laryngeal mask airway (LMA), figure 3, was designed by Archie Brain and first published in 1981. The aim of this radical innovation was to be more effective than the FM and less invasive than the ETT.[85] LMA is both a generic term and a brand name. Other designations include laryngeal mask (LM), supraglottic airway device

(SAD) or supraglottic airway (SGA). LMA is the most widely recognized acronym and will be used in this thesis.

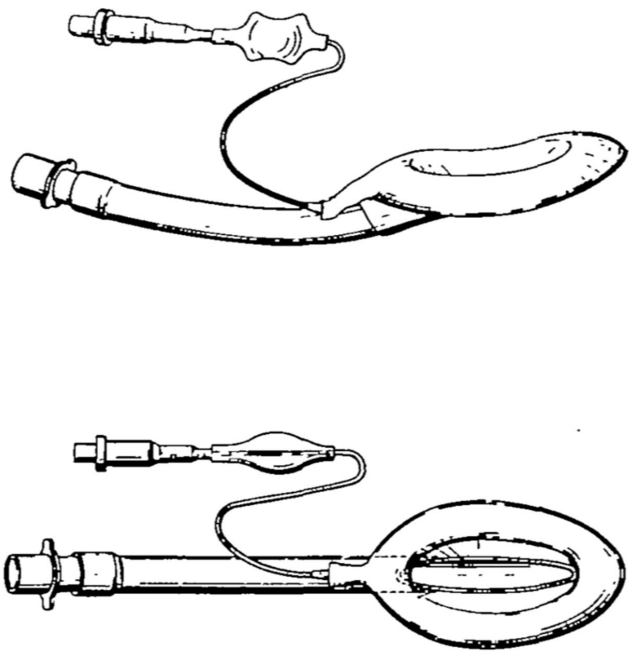

Figure 3. *Early prototype of the laryngeal mask. (With kind permission of Macmillan Press)*

In adults, anesthesiologists routinely use LMAs during surgical procedures. It has also gained popularity in pre-hospital resuscitations of adults in the hands of paramedics because it is easy to handle. New guidelines for neonatal resuscitation state that the laryngeal mask may be considered during resuscitation as an alternative to FM for PPV in newborns weighing >2000 g or delivered around or after 34 weeks of gestation.[74] In the case of neonatal resuscitation, previous observational studies, and one quasi-randomized study have shown that the LMA facilitated effective PPV in most of the treated infants (range 95-99%).[86] The potential advantages of using a LMA include the ease of insertion without a laryngoscope and minimal manipulation of the larynx.[82] Staff can use the LMA with a standard self-inflatable bag or a T-piece resuscitator. The first generations of LMAs required skilled operators, making it

harder to get an effective seal for lower cadre (non-doctor) birth attendants. Therefore, newer devices have been developed that are more user-friendly (figure 4).

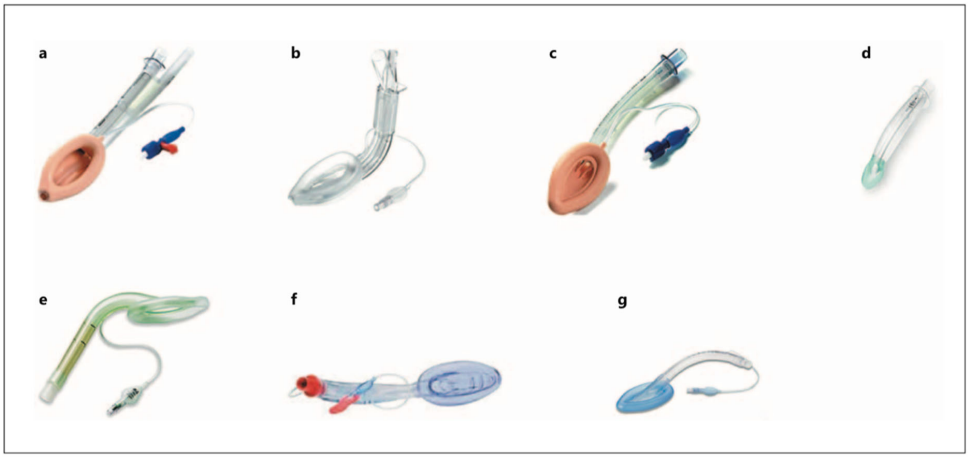

Figure 4. *Various LMA devices.* ***a*** *LMA Classic™* ***b*** *LMA Supreme™* ***c*** *LMA ProSeal™* ***d*** *i-gel®* ***e*** *Ambu®AuraOnce™.* ***f*** *Air-Q.* ***g*** *Shiley™ (With kind permission from Karger publishers)*

1.8.1 Conventional LMA

A neonatal LMA is built around an elliptical airway tube that allows easy placement. The interface with the larynx consists of a pre-curved cuff for an effective seal. The user places the LMA blindly along the palate of the patient until resistance is felt, as the tip fits in the top of the esophagus. After placement, the user inflates the cuff with air or saline fluid according to the size of the patient and administers PPV. In the Democratic Republic of Congo, training insertion with cuffed supraglottic airways on neonatal manikins with midwives and physicians had a high success rate of insertion.[87]

1.8.2 Uncuffed LMA: the i-gel

Dr Muhammed A. Nasir invented the i-gel® uncuffed LMA (Intersurgical Ltd, Wokingham, Berkshire, UK) after 19 years of research. It was approved for clinical practice in 2007 and is widely used in general anesthesia and pre-hospital care.[88] This single-use, latex-free LMA includes a unique cuffless design that fits tightly into the perilaryngeal framework. The interface is made of a soft, gel-like transparent

thermoplastic elastomer, which exerts a slight pressure on the pharyngolaryngeal structure and provides a seal without the need for an inflatable cuff[89] (figure 5 and 6).

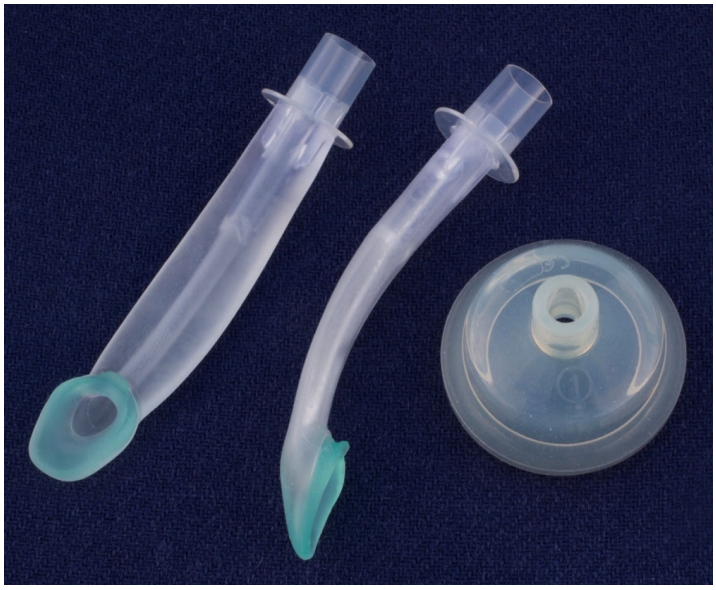

Figure 5. *The i-gel and the face-mask. (Photo: Thorkild Tylleskär)*

The smallest available i-gel is in size 1 and has been registered for use in neonates (2-5 kg). However, the design is made to fit even small-for-gestational-age infants and preterm infants (1-2 kg). A 1470 g baby was successfully resuscitated with a size 1 i-gel.[90] The main advantage of the i-gel is ease of placement because of small size and precurved shape. I-gel reduced insertion time from 18 to 13 seconds compared to a classic supraglottic airway.[91]

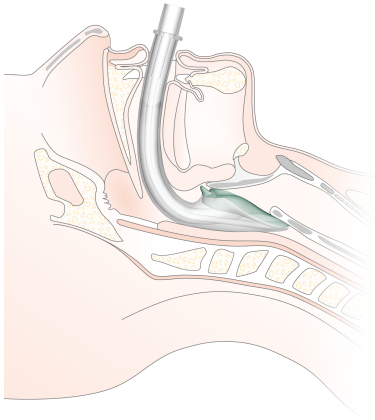

Figure 6. *Anatomical transect showing the position of the i-gel. (With kind permission from Intersurgical)*

Neonatal resuscitation research with uncuffed LMA has never been conducted, and any potential benefits remain unknown. The user-friendly design and innovative interface of the device could be particularly well suited for low-resource settings, were asphyxiated babies are often resuscitated by non-doctor staff.

2. Aim and objectives

The aim of this thesis was to investigate if midwives in low-resource settings could resuscitate newborn more effectively using a laryngeal mask airway instead of a conventional face-mask.

2.1 Specific objectives

1. To explore in a phase 1 preclinical manikin study, the ventilation performance and efficacy perception of participants without previous skills in the use of laryngeal mask airway (LMA) compared to face-mask ventilation (FMV) in a model (paper I).
2. To determine the effect of LMA on resuscitation time compared to FMV (paper II and III) including:
    - time to spontaneous breathing
    - ventilation time
3. To assess if the LMA can be safely task-shifted to midwives in a low-income setting (paper II and III) by describing:
    - Adverse events
    - Outcome at 48 h
    - Neonatal encephalopathy
    - Admission to the neonatal unit
    - Assistance of a supervising physician
    - Need for cross-over to an alternative airway after failed ventilation
4. To assess the physiological response of newborn receiving PPV with LMA compared to FMV (paper II and III) including:
    - heart rate
    - expiratory tidal volumes
    - mask leakage
    - positive inspiratory pressure
    - airway obstruction

3. Methods

The clinical research in this thesis consists of a series of trials (table 1 and figure 7). The objective of phase II and III randomized controlled trials was to establish the efficacy and of a medical intervention. A cross-cutting theme in the phase III trial (Annex) has been the opportunity to address specific questions such as monitoring respiratory function (paper III) and the use of a mobile phone app (NeoTap LS) in embedded sub-studies.

Table 1. *Design and participants*

	Design	**Participants**
Paper I	"Phase 1" trial: manikin study testing for safety	25 health workers
Paper II	Phase 2 trial: clinical pilot randomized controlled trial testing for efficacy and side-effects	49 asphyxiated newborns
Paper III	Phase 3 trial: clinical quasi-randomized controlled trial testing for respiratory function and heart rate response	48 asphyxiated newborns
Annex (study protocol)	Phase 3 trial: NeoSupra trial, a randomized-controlled trial testing for efficacy, effectiveness and safety	1150 asphyxiated newborns

3.1 Study setting and population

We conducted the research in this thesis at the Department of Obstetrics and Gynecology, Mulago National Referral Hospital in Kampala, Uganda. We chose this site mainly because of a long-standing academic collaboration between Makerere University, the University of Bergen and the Karolinska Institutet. The studies were motivated by previous research conducted at the site, which showed a high prevalence of brain injuries after birth asphyxia[51 92 93] and continued high rates of neonatal mortality (table 2), despite existing neonatal resuscitation training programs. Our local investigators were also experienced in data collection and the training of health staff.

Table 2 *Early childhood mortality rates 2002-2016 in Uganda adapted from the demographic and health survey 2016* [5]

Years	2002 - 2006	2007 - 2011	2012 - 2016
Neonatal mortality	24	28	27
Post-neonatal mortality [a]	45	25	16
Infant mortality	69	53	43
Mortality 1 - 4 years	51	32	22
Under-5 mortality	116	83	64

[a] Computed as the difference between the infant and neonatal mortality rate.

Figure 7. *Mulago National Referral Hospital, Kawempe division in Kampala, Uganda, there are ~25,000 deliveries per year. (Photo: Nicolas Pejovic)*

For paper I and II, we carried out the study in 2013 at the Operating Theatre of the Department of Obstetrics and Gynecology at Mulago National Referral Hospital. Mulago hospital is the National Referral Hospital for Uganda and a Teaching Hospital for Makerere University College of Health Sciences with a total of 28,759 total antenatal visits, 39,081 deliveries, and 11,120 postnatal visits in 2015. The neonatal special care unit has 42 cots, but cares for up to 110 infants. Mulago also serves as a general hospital for the Kampala metropolitan area, where the population is ~4.5 million. We performed both studies at the operating theatre where 15-30 cesarean sections – most of them on an emergency basis – were performed daily. A staff of 12 doctors (obstetrics and anesthesiology) and 13 midwives participated in the duty roster. Midwives and doctors in the delivery suite monitored most of the fetal heart rate using fetoscopy and hand-held Doppler fetal monitors. Newborn resuscitation was mostly performed by midwives, rarely by doctors. All staff participating in the study had received basic newborn resuscitation training and had had clinical experience of ventilating newborns with a face-mask. None of the team had ever used neonatal LMA in the unit. Positive pressure ventilation was performed on an average of 2 babies a day after an emergency cesarean section. Each of the 2 theaters had one basic resuscitation table without functional infant warmers. Oxygen (100%) could be delivered through nasal prongs after delivery in case of persistent cyanosis, generally without reliable pulse oximetry. The resuscitation equipment consisted of suction bulbs, self-inflating bags, and masks of varying sizes (all from Laerdal, Stavanger, Norway). Adequate equipment and skills for endotracheal intubation were rarely available. In cases of hypovolemia, intravenous fluids were delivered through peripheral intravenous lines. Embrace portable warmers were used to transport infants after resuscitation to the neonatal special care unit.

The NeoSupra Trial (Annex I) was carried out at Kawempe referral hospital, ~12 km north of the city center (figure 7). The hospital opened in 2016 and houses the delivery units of the Department of Obstetrics and Gynecology of Mulago National Referral Hospital, during the construction of the new Mulago Specialized Women and Neonatal Hospital. The staff delivered 24,434 live babies in 2018. Newborns participating in the study were recruited from one resuscitation area in the delivery

suite and 2 resuscitation tables in the operating theatres. Three research assistants and one supervisor were present at any time in the resuscitation area. The resuscitation area had the same standardized equipment as in the previous study, but the study team also cleaned and disinfected the equipment according to the HBB guidelines. A total of 150 midwives and doctors participating in the obstetric care at the hospital and took part in the study.

Paper III is a sub-study of the NeoSupra trial with detailed registration recorded on a limited number of infants included in the NeoSupra trial.

3.2 Participants

3.2.1 Paper I

Doctors, nurses, and midwives involved in neonatal resuscitation at the Labor Ward Theatre at Mulago National Referral Hospital.

3.2.2 Paper II-III and Annex

Inborn infants fulfilling the following inclusion criteria were eligible to participate in the trials: gestational age >34 weeks by best obstetric estimate (last menstrual period or ultrasound scan), expected birth weight >2000 g, need for PPV at birth and written parental consent. Exclusion criteria included major malformations or stillbirth.

3.3 Training

3.3.1 Paper I-II

A total of 25 participants working in the labor ward, including 12 doctors and 13 midwives and nurses, participated in an “on-the-job” Helping Babies Breathe (HBB) refresher course, including a training module for the use of LMA. We reviewed the HBB action plan, including the steps of stimulation, suction, and ventilation. The LMA training lasted 10 min and included a short lecture, a description of the LMA and the handling of the device, the insertion technique, and corrective measures in cases of failed insertion/ventilation. The LMA was lubricated before insertion in the manikin study. Skills training for the use of LMA and FM were practiced on a

manikin model, the SimNewB Laerdal (Laerdal, Stavanger, Norway), which provides realistic airways with anatomically correct pharyngeal structures and good feedback with chest-rise when effective PPV is provided. Thread sealing tape was added at connection points of the airways to ensure a leak-free system.

Figure 8. *Neonatal resuscitation training. (Photo: Nicolas Pejovic)*

3.3.2 Paper III and Annex

Two hundred and fifty midwives, doctors, and nurse-anesthetists involved in the care of neonates at Kawempe Hospital participated in a one-day modified HBB second edition course (figures 8 and 9), including a training module on the use of the LMA. Twenty-five participants and 5 facilitators participated in each session. Seven NeoNatalie inflatable manikins and 2 SimNewB high-fidelity manikin (both Laerdal manikin, Laerdal, Norway) were used to train the staff in the use of both devices (i-gel and FM). Facilitators used 2 newLifebox-R (Advanced Life Diagnostics, Weener, Germany) neonatal respiratory function monitor (RFM) at the skills training stations to improve the ventilation performance of the participants. The monitor provided feedback to the participants by displaying of airway leak (%), peak inspiratory pressure (cm H_2O), the

tidal volumes (ml/kg), and respiratory rate. We practiced corrective measures, such as repositioning of the FM or LMA, careful increase of the inspiratory pressure and adjustment of the respiratory rate. All participants had to perform 3 successful ventilation sessions with each device (= resulting in an appropriate chest rise) before being certified to take part in the trial. Refresher courses and simulation sessions based on the HBB action plan were offered on a monthly basis during the trial.

Figure 9. *Midwives newly certified as LMA-users. (Photo: Susanna Myrnerts-Höök)*

3.4 Randomization procedure

3.4.1 Paper I

Random assignment using sealed envelopes determined the order, starting with FM or LMA, in which participants ventilated the manikin.

3.4.2 Paper II:

We prepared a small opaque plastic container that concealed 25 white and 25 black toothpicks (figure 10). A study doctor randomly took a toothpick from the container at the beginning of each caesarean section. The color of the toothpick determined if FM or LMA would be placed on the resuscitation table. Should the baby need resuscitation and meet inclusion criteria, the toothpick was broken and discarded. If

not, the intact toothpick was placed back into the container. This randomization tool was proven to useful in a low-resource context with intermittent power cuts and limited space. This *no frills* approach could also be used in the broader context of emergency research, when time to randomization is critical. It also ensures a treatment balance between the 2 trial arms.

Figure 10. *Frugal engineering: the toothpick randomization container. (Photo: Nicolas Pejovic)*

3.4.3 Paper III

The design of the NeoSupra Trial posed particular challenges for the randomization process: 24/7 recruitment, resuscitations occurring in separate areas of the hospital and sometimes coinciding with each other. A day-by-day cluster randomization procedure was adopted so that all newborns enrolled on a particular day (representing a cluster) were randomized to the same treatment. An independent statistician prepared the randomization lists kept in sealed envelopes. A research assistant supervisor opened a new envelope each morning at 8.00 am and informed the midwives on duty of the assigned treatment. This method randomized daily groups of neonates rather than individual neonates. Sample size calculation took into account the clustering structure of the data.

Switch of device

Midwives performing resuscitation were recommended to use the assigned device for at least 3 min before considering switching the ventilation option from FM to LMA or vice-versa.

3.5 Equipment and data recording

3.5.1 Video monitor

We recorded all the resuscitations on video with a HD 1080P Black box AI-IP018 camera (Shenzen Aishine Electronics Co. Ltd, China) attached to a magnetic mount on the 3 available resuscitation tables (figure 11). The field of view was centered on the infant and the hands of the staff. Data were collected each morning from the camera's memory card and transferred to 2 separate hard drives. This method allowed precise assessment of a) ventilation time, b) HR, c) any assistance given by the supervising physician, and d) any switch to an alternative device. Time from birth to the beginning of resuscitation was registered by a research assistant (RA) with a stopwatch.

Figure 11. *Camera attached on magnetic mount. Casing concealed under duct tape to absorb shocks and discourage theft. (Photo: Nicolas Pejovic)*

3.5.2 NeoTap Life Support App

Heart rate measurement is critical for the evaluation of the asphyxiated newborn but may be inaccurate in the delivery room.[94-102] NeoTap Life Support (NeoTap LS) is a mHealth (mobile health) application that was designed by members of the research team (SM, NP) to measure neonatal heart rates. It was developed by the non-profit organization Tap4Life (Stockholm, Sweden) both as a research tool and clinical monitoring device for low-resource settings. A major feature of NeoTap LS (figure 12) is a precise algorithm-based assessment of the HR.[103] Research doctors used the NeoTap to collect HR data during resuscitation by listening to the heart with a stethoscope and simultaneously tapping the screen of a smartphone. This method allowed intermittent assessment of the HR during resuscitation with the output being visible on a video display. Research assistants and study doctors received phones preloaded with beta software versions during the trial preparation. Agile software development allowed us to continuously modify the design, interface, and features of NeoTap LS after user feedback and video analysis, which resulted in the integration of a package of additional features, such as:

- Checklist for equipment
- Resuscitation timer
- Color-coded heart rate and breathing rate monitor
- Fetal heart rate monitor
- NeoPacer (acoustic and visual ventilation support)
- Automated Apgar score calculation
- Clinical tutorials
- Referral decision support
- Danger sign assessment
- Free global download on Google Play and App Store

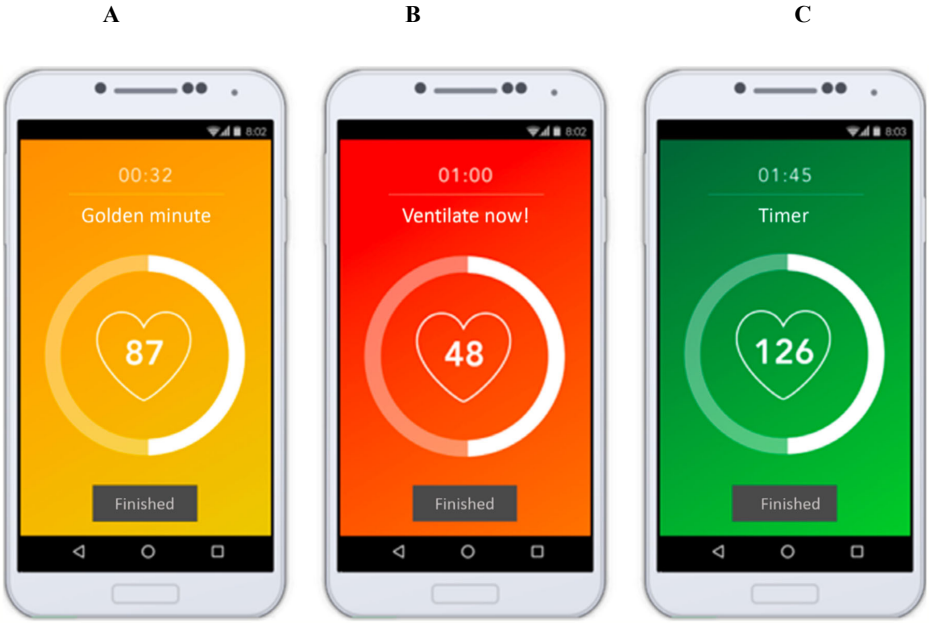

Figure 12. *(A, B and C) The NeoTapLS as displayed on the phone screen. Heart rate is registered by tapping at least 3 times on the screen. (A) Heart rate at 32 seconds <100 (yellow screen), prepare for ventilation. (B) Heart rate at one minute <60 (red screen), ventilate now! (C) Heart rate at one minute 45 seconds >100 (green screen), ventilation is satisfactory.*

Dr Susanna Myrnerts-Höök collected data for additional sub-studies of the trial that will help us understand how this tool could improve the quality of newborn resuscitation.

3.5.3 Electrocardiogram (ECG)

A dry-electrodes ECG (NeoBeat Newborn Heart Meter, Laerdal Global Health, Stavanger Norway) was used to collect HR data[48 104] (figure 13). When not in use, the unit rests on a mounted charging stand. The NeoBeat is placed on the chest of infants prior to ventilation and HR is obtained within a few seconds on a backlit display. The monitors display continuous HR data from the start of ventilation.

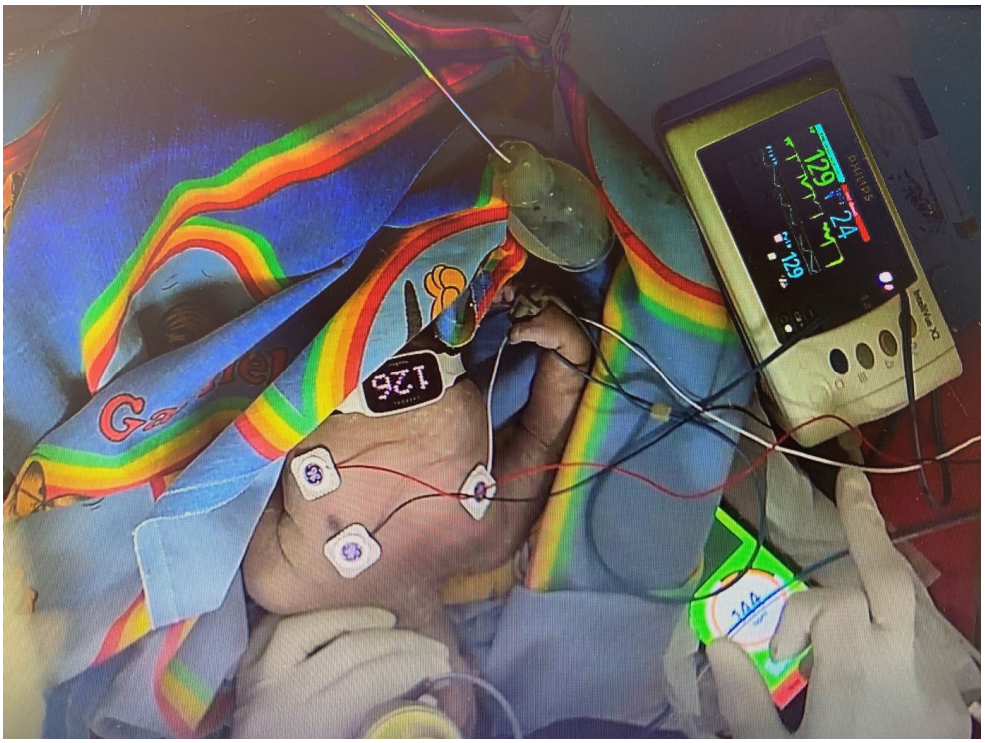

Figure 13. *Heart rate recorded simultaneously with NeoBeat (device on the chest of the baby), regular ECG (Philips IntelliVue X2 to the right) and NeoTap LS (lower right, partly hidden). (Photo: Nicolas Pejovic, with kind permission from the parents)*

3.5.4 Respiratory function monitor

Respiratory function monitoring (RFM) is rarely used in the delivery room but can be a useful tool for assessing the quality of ventilation of the newborn.[104-115] The NewLifebox-R (Advanced Life Diagnostics, Weener, Germany) neonatal monitor (figure 14) was used for RFM. This compact unit is very accurate[116] and can function autonomously for several hours (figure 14). A variable orifice pneumotachometer (Avea VarFlex Flow Transducer, Vyaire Medical, Yorba Linda, USA) measured airway pressure and flow between the self-inflating bag and the FM or LMA. The probe only added 0.7 mL dead-space to the system. The RFM integrated the pneumotachometer signals and displayed the inspired tidal volume (Vti) and expired tidal volume (Vte), leak (%) and peak inspiratory pressure (PIP). A separate monitor displayed the data outside the resuscitation area and recorded data on an SD card.

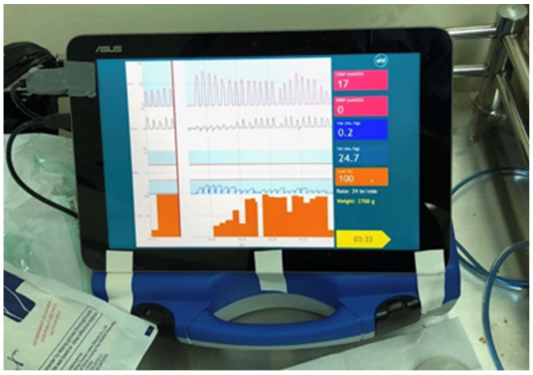

Figure 14. *The respiratory function monitor used in the study. (Photo: Nicolas Pejovic)*

3.6 Data collection and management

Research assistants and trial investigators collected the perinatal data on pre-coded case report forms (CRFs) bedside by consulting clinical charts and after interviewing mothers to the recruited participants after labor. Observations during resuscitation were timed with a stopwatch. Video review of the resuscitations provided additional resuscitation data and quality control of the interventions. Research doctors collected HR data.

3.6.1 Paper I

In this manikin study, health staff that participated in the training were asked to place each of the 2 devices (LMA and FM) on 3 consecutive occasions as they were timed with a stopwatch. The time to establish a chest rise on the manikin was recorded by a single unblinded observer from the moment when the FM/LMA was picked up. The success rate was determined by successful ventilation occurring within 30 seconds. A maximum of 2 new attempts was carried out in the case of failure. Participants evaluated the ease of application and ventilation on a five-point Likert scale: 1 for insufficient, 2 for sufficient, 3 for fair, 4 for good and 5 for excellent. Desirability bias was mitigated by informing participants of the aims of this comparative study *after* their involvement. Data was entered in an Excel database and analyzed using the statistical package STATISTICA, StatSoft version 6 (www.statsoft.com).

3.6.2 Paper II

In this pilot clinical trial, data was collected and managed by a team consisting of 3 investigators, 2 research assistants and 1 data entry manager. The research assistants collected the perinatal data on pre-coded case report forms (CRFs) bedside by consulting clinical charts and interviewing mothers to recruited participants after recovery from cesarean sections. Clinical outcome data of participants was collected on paper CRFs by both research assistants at 24 and 48 h.

PPV with FM or LMA was initiated in the case of apnea and/or gasping at 1 min of birth. PPV was administered with a 230-mL silicon self-inflating bag with a pop-off valve limit at 40 cm H_2O connected to a silicone, round-shaped FM (both Laerdal Medical, Stavanger, Norway). Health staff applied corrective measures according to the MR SOPA strategies in case of inadequate ventilation. PPV was continued until spontaneous breathing was established.

All resuscitations were video recorded by a camera attached to a mount on the resuscitation table. Clare Lubulwa (CL), co-investigator and supervising physician collected HR data by auscultating the heart at set time intervals, using NeoTap LS on an android tablet. Data was collected after each resuscitation from the cameras memory card and transferred to 2 separate hard drives. Video review allowed precise assessment of time to spontaneous breathing, ventilation time, HR, assistance by supervising physician, and switch to an alternative device. Time from birth to the beginning of resuscitation was registered by a RA using a stopwatch. Data from resuscitation and paper CRFs was entered separately into an Excel database by 2 investigators. Non-matching data was assessed after video review by a third investigator. The clean data set was entered separately and analyzed by the statistician (FC) using R V.3.2.2 software (R Foundation for Statistical Computing, Vienna, Austria).

3.6.3 Paper III and Annex

In the NeoSupra trial, data was collected and managed by a team consisting of 3 investigators, 18 research assistants (Paper III and Annex) and 2 data entry managers.

Observations during resuscitation were timed with a stopwatch. Video review provided additional resuscitation data, including ventilation time, any assistance by supervising physician, any switch to an alternative device and any need for advanced resuscitation. Time from birth to the beginning of resuscitation was registered by a RA using a stopwatch. HR data was collected at the start of ventilation by placing the frame of the dry-electrode NeoBeat on the chest of a newborn infant not responding to stimulation. The RFM sensor was placed between the self-inflating bag and the device, and PPV delivered by the same principles as described above (paper III).

The local trial manager and research assistant supervisor, reviewed the paper CRFs and resuscitation videos on a daily basis for quality control assurance. Weekly meetings were held with the research assistants (RA) to correct for inconsistency and missing information. Regular meetings were held with the RAs to maintain the quality of the data collection. RAs were retrained in cases of protocol violation. Data were doubly entered into Open Data Kit (ODK, https://opendatakit.org), an open-source tool for mobile data collection (NeoSupra trial and Paper III) by the 2 data entry managers from the paper CRFs. Data-cleaning was performed by a co-investigator and non-matching data corrected after review of the scanned CRFs. The clean data set was transferred to a statistical software package for analysis, with the data stored on an encrypted server that could only be accessed by the main investigators.

3.7 Statistical analysis

3.7.1 Paper I

A convenience sample of staff participating in newborn resuscitation was included in the study, and no sample size was calculated. Each individual staff member consented to participate.

Paired t-test, and unpaired t-tests were used to determine the difference between the LMA and FM regarding the success rate of insertion, mean time to successful

ventilation, perceived ease of insertion and perceived effectiveness of ventilation. $p<0.05$ was taken as significant.

3.7.2 Paper II

The sample size was determined in accordance with the only large study on this topic.[86] We expected a longer time to spontaneous breathing with FM compared to LMA. Moreover, we estimated the time to spontaneous breathing to be longer in our sample because of delays in delivery and difficulties in assessing fetal distress at Mulago Hospital. Time to spontaneous breathing was modelled with gamma distribution as right-skewed data of duration. In accordance with local clinical observations and available information in a similar setting, we estimated a mean time to spontaneous breathing of 210 s. A sample size was estimated at 25 subjects in each arm with a power of 0.80. This sample size was also considered appropriate for a task-shifting trial emphasising safety aspects when involving midwives for the first time in advanced airway management.

The Fisher's exact test was used to compare categorical data between the 2 arms. Data were expressed in numbers and as percentages. The Mann-Whitney test was used to compare birth weight (expressed as median and IQR). Time to start of PPV, spontaneous breathing, and ventilation time were modeled with gamma distribution and the observed duration data were summarized as means and SDs. The effect of LMA and FM on duration data was assessed using a gamma model. HR data were collected at specific time intervals during resuscitations and expressed as mean and SD. The effect of the device on HR was determined by a linear mixed effect model accounting for the longitudinal structure of the data. $p < 0.05$ was considered significant.

3.7.3 Paper III

A sample size of 46 newborns (23 per arm) was required to have a 0.9 chance of detecting a mean difference of 20% (SD 20) in the primary outcome measure (mask leak during first 60 breaths) at a significant ($p<0.05$) level between the 2 arms.

Continuous data were compared between the 2 arms using Student's t-test or Mann-

Whitney test, as appropriate. Categorical data were compared between the 2 arms using Fisher's test. Continuous data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), while categorical data were expressed in numbers and as percentages.

We evaluated the HR measures over time with a random regression model, including arm, time and an interaction term arm*time. The tests were 2-sided, with $p<0.05$ being statistically significant.

3.8 Ethical considerations

All the individual staff members in the manikin study (paper I) consented to participate in the study. The trials in papers II, III and Annex were approved by the Institutional Review Board (IRB) of Mulago National Referral Hospital, Uganda, the Uganda National Council of Science and Technology, the Director-General from the Ministry of Health, Uganda and by the Regional Committee for Medical and Health Research Ethics in Norway, No 2013/2096 and 2017/989.

3.8.1 The consent process

In paper II, oral and written information was obtained from the mother and relatives upon maternal admission. A senior investigator was available on the wards to discuss any queries concerning the trial. Informed written consent was obtained prior to delivery by a parent or caregiver before admission to the operating room.

In paper III and annex, a 2-tiered consent procedure was implemented in this trial after extensive discussions with the ethical review board. A recent study in the pediatric emergency department had also used a similar procedure.[117] The provision of basic written and oral information about the trial was given from dedicated research assistants to all mothers that entered the labor ward. Oral consent was sought unless the mother was too ill or distressed. A senior investigator was available at any time to discuss further questions concerning the trial. A full written deferred consent that included all required elements of a regular consent was subsequently obtained from the parent(s) of infants recruited after resuscitation.

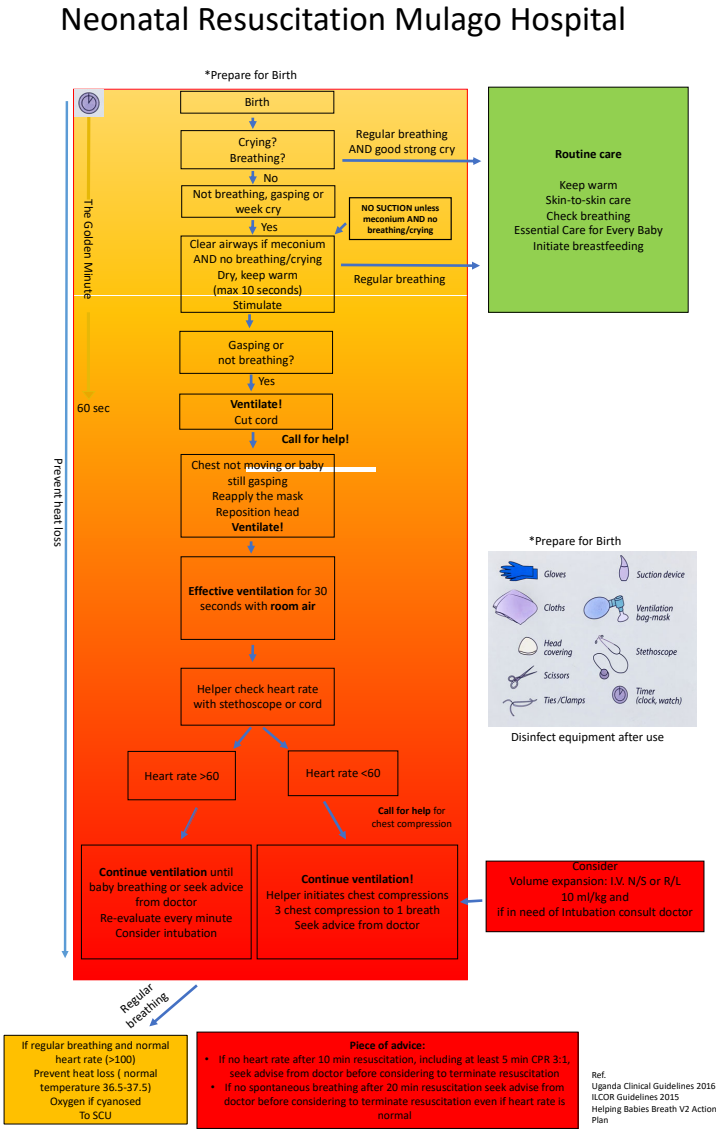

Figure 15. *Neonatal resuscitation chart for Mulago Hospital, based on ILCOR 2015 guidelines and HBB second edition*

3.8.2 Discontinuing resuscitation

According to the ILCOR international consensus on neonatal resuscitation[74] and Mulago Hospital neonatal resuscitation guidelines (figure 15), health staff was recommended to terminate the resuscitation if there was no perceptible heart rate after

10 min or no recovery of spontaneous breathing after 20 min, even if the heart rate was adequate.

3.8.3 Safety and harms

Standard operational procedures (SOPs) for detection and reporting of adverse events (AEs) and serious adverse events (SAEs) were implemented at the study site before the start of the trial. Compliance to the protocol and the neonatal resuscitation action plan were rehearsed during dry runs prior to the start of the trial. Baseline data from the hospital was recorded, and procedures discussed with staff and clinical heads of the departments of Obstetrics and Pediatrics. Safety measures included reporting of SAE in the case report forms (CRFs) used for data collection, and monitoring of the resuscitation area with video and detection of unexpected changes in the incidence of common neonatal complications. The research assistants participated in weekly audits aimed at improving the quality of clinical work and identification of possible SAEs. All SAEs, regardless of a suspected causal relationship with the intervention, were reported within 7 days to the Mulago Research and Ethics Committee (MREC) to guarantee the safety of the participants. Any Suspected Unexpected Serious Adverse Reactions (SUSARs) with or without a reasonably plausible causal relationship with the use of the LMA were also reported to the MREC.

4. Main findings

4.1 Teaching ventilation with LMA in a manikin model

The first study in this thesis compared the use of the LMA with FMV, the standard of care in low-resource settings. A manikin-based training module was integrated in an HBB refresher course. Twenty-five healthcare providers (12 doctors and 13 midwives and nurses) participated in the study. LMA was significantly better compared to the FM in establishing effective PPV ($p<0.001$) and had a 100% success rate in providing chest movements to the manikin within 30 s (table 3).

Table 3. *Insertion success rate, mean time to successful ventilation, perceived ease of insertion and perceived effectiveness of ventilation with LMA and FM.*

	LMA N = 25	**FM** N = 25	**p value**
Success rate	n (%)	n (%)	
1st attempt	25 (100)	18 (72)	<0.001
2nd attempt	25 (100)	23 (92)	<0.001
3rd attempt	25 (100)	20 (80)	<0.001
Mean time to successful ventilation	Mean ± SD	Mean ± SD	
1st attempt (seconds)	6.2 ±2.3	8.3± 4.7	0.18
2nd attempt (seconds)	5.2 ±1.1	9.9± 14.1	0.68
3rd attempt (seconds)	4.5 ± 1.0	6.6 ± 5.9	0.38
Ease of application/ ventilation	Median ± SD	Median ± SD	
Score (one lowest, five highest)	4.7 ± 0.4	3.3 ± 0.8	<0.001

4.2 Task-shifting the use of LMA to midwives in low-resource settings

At Mulago hospital, midwives with no experience of advanced airway management could learn to ventilate effectively a manikin after a 5 min training module. The user satisfaction on a 5-point Likert scale was 4.7 in the LMA compared to 3.3 with the FM (paper I).

Two experienced study doctors supervised newborn resuscitations in this first task-shifting trial involving midwives using LMA (paper II). Forty-two resuscitations were performed by midwives (21 in LMA group and 21 in FM group), whereas the remaining 7 (14%) were carried out by physicians (4 in LMA group and 3 in FM group). All newborn infants were born after an emergency caesarean section. Supervisor assistance was required in 13% of resuscitations with LMA and 24% of resuscitations with FM. Conversion to the other device because of poor response was done in 0% of the LMA group and 44% in the FMV group. No adverse events, such as bleeding, laryngospasm or vomiting, were reported in either group. There was no difference in outcome at 48 h between the groups. Thirteen patients were admitted to the neonatal unit (5 in LMA arm and 8 in FM arm), one patient died and 2 patients had moderately/severe hypoxic ischemic encephalopathy in the FM arm.

In paper III, resuscitations were performed by midwives without direct supervision. Forty-six infants (23 in the LMA group and 23 in the FM group) were included in the study. Conversion to an alternative airway was done in 4% of the LMA group and 26% of the FMV group. No side-effects reported in the FMV group, but there were 4% (1 case of mouth bleeding, with good clinical outcome) in the LMA group. Outcome data at 7 days will be published in the main study (Annex I).

4.3 Effect of LMA on resuscitation time compared to FMV

In paper II, PPV started after a mean of 64s (60s in LMA arm and 68s in FM arm; p=0.26). Mean time to spontaneous breathing was 153s (SD 59) with LMA and 216 s

(SD 92) with FM (p=0.005), a mean reduction of 31% (95% CI 11% to 44%). Total ventilation time was also shorter in the LMA group than in the FM group (mean 93s vs 140 s, p=0.02; Table 4).

In paper III, ventilation started at a median 39 seconds after birth (IQR 25-68) and lasted a median of 95 seconds (IQR 63-180) in the LMA group and 197 seconds (58-662) in the FMV group, with no statistical differences between arms (p=0.99 and p=0.22).

Table 4. *Time to start of ventilation, ventilation time, assistance by supervisor and conversion to alternative device by trial arm.*

	LMA N = 24	**FM** N = 25	**p-value**	**Effect of the intervention**
Start of PPV (s) [a]	60 (11)	68 (36)	0.26	0.88 (0.70 to 1.10) [b]
Ventilation time (s) [a]	93 (52)	140 (90)	0.02	0.67 (0.47 to 0.93) [b]
Assistance from the supervising physician [c]	3 (13)	6 (24)	0.46	0.46 (0.07 to 2.52) [d]
Conversion to alternative device [c]	0	11 (44)	0.0002	0.00 (0.00 to 0.29) [d]

Data is expressed as [a] mean (SD), [b] mean ratio (95% CI), [c] n(%) or [d] odds ratio (95% CI)

4.4 Respiratory function during resuscitation of asphyxiated newborn infants with LMA

In paper III, the respiratory function was analyzed during the first 60 breaths to avoid contamination between arms. Mean mask leak was 46% (SD 24) in the FM arm and 39% (SD 20) in the LMA arm (p=0.32). Peak inspiratory pressure (PIP) was 34.5 cm H_2O (SD 8.2) in FM and 39.4 cm H_2O (SD 7.6) in LMA (p=0.04). Mean expiratory tidal volume was 8.8 ml/kg (SD 5.8) in FM arm and 8.2 ml/kg (SD 3.4) in LMA arm (p=0.66), whereas mean inspiratory tidal volume was 16.2 ml/kg (SD 8.0) in FM arms and 15.6 ml/kg (SD 5.6) in LMA (p=0.77).

Table 5. *Respiratory function by trial arm.*

	LMA N = 23	**FM** N = 23	**p-value**
Time to start ventilation (s) [a]	36 (27-73)	45 (25-62)	0.99
Ventilation time (s) [a]	95 (63-180)	197 (58-662)	0.22
Mask leak during first 60 breaths, % [b]	39 (20)	46 (24)	0.32
Expiratory tidal volume during first 60 breaths, ml/kg [b]	8.2 (3.4)	8.8 (5.8)	0.66
Peak inspiratory pressure during first 60 breaths, cm H_2O [b]	39.4 (7.6)	34.5 (8.2)	0.04

Data is expressed as n (%) [a] median (IQR), or [b] mean (SD)

4.5 Heart rate response during resuscitation with LMA and FMV

In paper II, HR increased during the first 240s after birth ($p<0.0001$) and was higher in the LMA arm than in the FM arm ($p=0.0006$). The rate of increase was similar in the 2 arms ($p=0.48$). The proportion of patients with HR <100 bpm decreased in both arms from ~80% at 30s after birth to 4% at 240s.

In paper III, HR rate was higher in the LMA than the FM arm ($p=0.05$) and increased during the first 60 breaths ($p<0.0001$), but the difference between the LMA and FM arms reduced with time ($p=0.04$). In 26 infants with HR<100 bpm at start of ventilation, a shorter time was needed to achieve HR>100 bpm in LMA (median 13 seconds, IQR 9-15) in comparison to the FM arm (median 61, IQR 33-140; $p=0.0002$).

4.6 Needs for alternative airway

In paper II, all procedures were effective in the LMA arm, whereas 11 participants receiving FM were switched to LMA after 150 s because response to FMV was deemed unsatisfactory by the supervisor due to poor HR response and/or lack of chest rise ($p=0.0002$).

In paper III, 3 infants in the FM arm and none in the LMA arm were converted to the alternative device due to the continued unsatisfactory response after 3 min of resuscitation (p=0.23). Advanced resuscitation was needed in 3 infants in each arm (p=0.99). Intubation was needed in one LMA infant and 3 FM infants (p=0.60).

4.7 The importance of airway obstructions

Routine suctioning of the airways was performed on 56.6% of the FMV group and in 52.2% of the LMA group in the 46 participants in paper III. Median suction duration was 30 seconds (IQR 23-42) in the LMA arm and 29 seconds (IQR 11-41) in the FMV arm (p=0.62). Complete or partial obstruction of the airways with poor chest movements, expiratory tidal volumes <4 ml/kg and/or persistent bradycardia was recorded in 47.8% of FMV cases and 17.4% of cases LMA.

Table 6. *Participants in need of rescue suctioning.*

	LMA N = 23	**FMV** N = 23
Poor/absent chest movement at 30 s	2	11
Suction rescue	4	6

Data is expressed as n (%)

Response to corrective measures (mask reposition, oral suction and increased ventilation pressure) failed for 26.1% in the FMV group and 17.4 % in the LMA group (table 6). Deep oral and/or tracheal suctioning using laryngoscope with a modified Laerdal Penguin (figure 16) improved heart rate and expired tidal volumes in all treated participants. These observations were not part of the original paper.

5. Discussion

The studies in this thesis provide valuable data on a number of points that will be discussed in the following order:

a) a manikin-based training model for implementation of neonatal resuscitation with LMA,
b) safety of task-shifting the use of LMA to midwives performing newborn resuscitation,
c) the effect of LMA compared to FM on total resuscitation time and heart rate response,
d) effect of LMA compared to FM on leak and tidal volume delivery,
e) the rate of apparent failed ventilation due to leak or airway obstruction and necessitating alternative airways.

All the interventions evaluated could be implemented in low-resource settings where most deaths and disability from birth asphyxia occur.

5.1 Teaching ventilation with LMA in a manikin model

In the preclinical manikin study, we found that the use of LMA could be taught easily to healthcare workers in low-resource setting within the framework of the HBB curriculum. The PPV performance was better with the LMA and the participants found the LMA much easier to use.

Training models for the use of LMA in newborn have not been extensively investigated. In adult bedside training models, LMA insertion could be taught to unskilled personnel and achieve the same high level of success (94%) as skilled personnel (98%).[118] Brief manikin-only training (<15 min) in high-resource settings have reached 100% insertion success in neonatal models[119 120], and our data are in agreement with these findings. The participants completed an LMA training module (<15 min), and could all establish PPV on the first attempt. In contrast, 7/25 participants (18%) failed to establish PPV with FMV within 30 seconds. It is

noteworthy that all participants were experienced FM users and had received repeated HBB and/or Newborn Life Support (NLS) training. This could imply that high-dose refresher training for LMA insertion skills might not be as critical as for FMV, but resuscitation involves not only the insertion technique. Future studies will be needed to address this aspect before implementation of LMA as an interface for newborn resuscitation.

Heath staff unfamiliar with LMA may prefer FMV in the delivery room, but this may change after training. In their LMA manikin trial, Gandini et al. (2004) found the preferred technique for neonatal resuscitation reversed from 6% to 80% after a training session. Zanardo et al. also found higher approval rate for LMA resuscitation compared to FMV after manikin-training in a low-resource setting.[121] Our study also reported a higher effectiveness score (ease of application/ventilation) for the LMA perceived by the participants delivering PPV in the manikin.

The i-gel LMA was chosen for this study. It is the only device on the market with a solid gel cushion replacing the inflatable cuff. The advantage of this design is ease of use. The extra equipment and time necessary for manual cuff inflation in alternative devices may delay the start of PPV, but this aspect needs to be investigated. A recent manikin study compared 7 different neonatal LMAs available on the market. The i-gel LMA was rated as easy to insert by 100% of the participants. The corresponding rates for the 6 other devices ranged from 40 to 95%.[32]

This study has some of the limitations expected from manikin studies in regard to translation of skills acquired during simulation-based training into clinical practice. The study was conducted at the labor ward theatre and the number of participants was limited to 25, so the results could not be stratified according to work categories. On-the-job training was conducted for practical reasons and pre- and post-training knowledge assessment was not performed. Despite these limitations, an evaluation of PPV performance of midwives with LMA on the manikin was crucial before bringing this new resuscitation tool into clinical practice.

5.2 Safety and task-shifting

The trials (paper II and III) demonstrated for the first time that midwives could safely perform newborn resuscitation with LMA. We used high-definition video recordings to collect resuscitation data that included any interventions from supervisor, switch to alternative device after failed PPV, and monitoring indicated adverse events. The cameras in paper II were manually operated; however, this minor disturbance did not interfere with clinical activity. The video monitors in paper III were automated. The staff and research assistants participated in weekly meeting when difficult cases were discussed. The trial team gave constructive feed-back in cases when detrimental practices were observed, such as excessive stimulation or prolonged suctioning of the airways. These issues will be discussed as potential bias in chapter 5.7.7.

The LMA was introduced in clinical practice >30 years ago and has become an indispensable airway management tool in the hands of anesthesiologists. Task-shifting the use of an LMA device to non-doctor or inexperienced health staff in resource-limited settings could be a way of improving the outcome of newborn resuscitation. In Mozambique, 90% of the caesarean sections at the district hospital level are performed by non-doctors without a significant difference in outcome compared to medical doctors.[122] There is a lack of high-quality evidence assessing whether the skills acquired from LMA insertion on the manikin translates into clinical practice. Two experienced study doctors supervised newborn resuscitations in the first task-shifting trial involving midwives using LMA (paper II). Bedside supervision included practical advice, corrective measures to improve ventilation and hands-on assistance where required. Interventions were required in 13% of resuscitations with LMA and 24% of resuscitations with FM. Switch to the alternative device was advised after 180s in case of poor chest rise and/or heart rate response, despite corrective measures.

Nearly half (44%) of the neonates did not respond well to FMV within the first 2 min of ventilation. Shifting to LMA resulted in successful resuscitation. No participant in the LMA group had to be converted to FMV.

In paper III, resuscitations were performed by midwives without direct supervision. Conversion to an alternative airway was less frequent, and occurred in 4% of the LMA group and 26% of the FMV group. We opted to offer all participants in the trial the best possible resuscitation practices available for low-resource settings. The staff had received a full-day training course focused on airway management. Detrimental suction practices observed in the previous study were discussed and discouraged. Research assistants prepared and sterilized the resuscitation equipment after each use.

Drake-Brokeman et al. published in the Lancet (2017) adverse event data from a large RCT that compared the use of LMA vs. endotracheal tubes in pediatric anesthesia.[84] Patients managed with endotracheal tubes were nearly 5 time more likely to have adverse events (19%) compared to LMA (4%). This has been announced as a paradigm shift, should the results be confirmed.[84] Both our studies also reported a very low rate of adverse events. In paper II, no adverse events such as bleeding, laryngospasm or vomiting were reported in either group. In paper III, no adverse events were reported in the FMV group and 4% in the LMA group (1 case of mouth bleeding with good clinical outcome). The LMA appears to be safe even in the hands of non-doctor staff. The level of bedside supervision after manikin training needs to be clarified. Data from the NeoSupra trial will help us understand if LMA resuscitation can be implemented safely without formal clinical supervision.

5.3 Ventilation time

Based on our papers II and III, the LMA may be more effective than FMV in terms of shorter ventilation times; time to spontaneous breathing and total ventilation time were consistently shorter in the LMA arm compared to the FM arm. Researchers commonly use stopwatches to register ventilation time during resuscitations but the stressful situation increases the risk for mistakes. Instead, we assessed the ventilation time by video review with 2 separate observers (paper II and III) and RFM (paper III). Non-matching data was reviewed a third time. Ventilation time was shorter in the LMA groups, 93 s (paper II) and 95 s (paper III), compared to the FM group, 140 s (paper II) and 193 s (paper III). The interquartile range (IQR) in the FMV group

(paper III) was very large (58-662) and the small sample size presents obvious limitations. The results, however, are in line with previous studies, including a Cochrane review in 2018, that showed that PPV was more effective with LMA compared to FMV (paper II).[123] Resuscitations in previous studies were all performed by doctors using traditional LMAs with an inflatable cuff.[121 124-128] Our results suggest that even in low-income settings, non-doctor staff can improve aeration of the lungs using uncuffed LMAs and potentially shorten the hypoxic process. Ersdal et al. in a study from Tanzania reported that 30 s delay in initiation of PPV increased mortality and morbidity by 16%.[37] Reduction in ventilation time could have a similar impact. This aspect will be investigated in the NeoSupra trial (Annex I). PPV is interrupted for > 30% of the total ventilation time, even in high-resource settings.[129] Shorter ventilation time could be the result of fewer interruptions during LMA ventilation since the mask does not need to be repositioned and the fact that the operator actually needs to actively hold the bag for as long as it is connected to the LMA. Another important aspect is that PPV with LMA can be delivered with just one hand. This allows the caretaker to reposition or transport the baby without interrupting PPV. which may be crucial in understaffed setting were midwives may need to resuscitate the baby beside the mother.

5.4 Heart rate response

The LMA also provided a faster HR recovery during resuscitation in our clinical trials (paper II and III). A rapid increase of HR in the asphyxiated babies is considered the best indicator of adequate ventilation.[74 130 131] A HR <100 is one of the thresholds for starting PPV. The HR will rise rapidly in particular if an infant is in primary apnea and/or receives efficient PPV. Severely compromised infants with secondary apnea and/or suboptimal ventilation will experience a more gradual rise of HR. In the first clinical study (paper II), HR increased faster in the LMA group during the first 240 s after birth. HR data was collected with the NeoTap LS for practical reasons, but the method had not been validated at the time of the trial. Another limitation is that HR was not collected at the start of PPV, but at fixed 30 s intervals after birth. HR registration was improved in the subsequent study (paper III)

with additional ECG data collected from beginning to end of PPV. We recorded HR data continuously and registered changes of 5 bpm or more. Twenty-six infants had a HR<100 at start of ventilation. The data showed a similar faster increase in HR in the LMA group. The time to achieve a HR >100 was dramatically shorter in the LMA group median, 13 s compared to the FMV group with a median of 61 s (p=0.0002). It is unclear if the improved HR response is the result of more efficient PPV from the LMA, less interruptions of PPV during LMA ventilation, or other factors such as sympathetic stimulation from the LMA insertion. Results may also have been influenced by a shorter time to start ventilation in the LMA group in paper III (p=0.99).

Increased heart rate response has been linked to higher delivered Vte.[114 132] Tactile stimulation of the oropharynx region can also elicit a sympathoexcitative response in the human.[133] Anecdotal observations from the video review reveal that some infants react with a HR increase at the moment of LMA insertion *before* initiation of PPV. On the other hand, application of the face-mask could have activated the trigeminal nerve, known to induce bradycardia and inhibit breathing[134 135] Autonomous HR response during PPV with various interface requires further investigations.

5.5 Mask leak and tidal volumes

The LMA used in resuscitation provided similar mask leak and Vte compared to FMV (paper III). To our knowledge, this is the first clinical report evaluating respiratory function during newborn resuscitation with LMA. Tracy et al. (2018) recently published a manikin trial that compared the i-gel uncuffed LMA with face-mask and 6 other LMA designs. Mean mask leak in the i-gel was only 4%, whereas the leak from other devices ranged from 35-44% for the FM and 46-65% for the different LMA designs.[136] In our clinical study, the mean mask leak with i-gel was 39%. Mask leak from the FM, on the other hand was 46%, similar to the manikin data and a recent clinical trial from Tanzania.[114] The large difference in LMA leak between manikin and clinical data was unexpected, but results from simulated models can be misleading. Accurate anatomical details are just one of the many parameters.

Tissue moisture, airway compliance, fluid in the alveoli, and natural resistance from cartilage and bony structures also need correct modeling if high-fidelity manikins are to be improved. The causes of leak in FMV are well understood and include mask leak at the rim, head positioning, laryngeal adduction, blockage of nose and mouth from excessive pressure and pharyngeal obstruction by the tongue.[137] Causes for LMA leak are not as well investigated. Oropharyngeal leak (or seal) pressure is an essential characteristic of LMA as it determines the pressure threshold when the LMA starts leaking at the interface. The mean oropharyngeal leak pressure reported for the i-gel in pediatric anesthesia ranges between 20 and 27 cm H_2O and compares favorably to other devices.[138] The mean PIP delivered by the self-inflating bag during LMA ventilation was 39.4 cm H_2O. The high mean pressure could be caused by users blocking the pressure-release valve or forcefully compressing the bag. Leakage at this pressure level might be useful if caused by excessive PIP and could protect the infant's lung from barotrauma caused by high Vte.[139] However, excessive mask leak (>60%) occurred in 17.4% in the LMA group and 30.4% of the FM group and was associated with low Vte (<5 ml/kg). Oropharyngeal leakage and gastric insufflation in LMA has been described in pediatric anesthesia and can be the result of a misplacement of the LMA, with the tip of the device inserted into the entrance of the esophagus.[140] We also observed occasional cases were the LMA was unintentionally rotated or twisted from the vertical axis. The staff practiced corrective measures that included a slight retraction of the LMA in the case of absent chest movements and/or gastric distention during the training. Additional review of the video data could help us determine if these actions were translated into clinical practice.

Mean Vte was 8.8 ml/kg in the FMV group, 0.6 ml/kg more than the LMA group ($p=0.66$) despite a smaller leak ($p=0.32$) in the LMA compared to FM. Van Vonderen et al. also reported lower Vte in preterms receiving PPV with ETT compared to FMV and speculates that FMV pressurizes the highly compliant oropharyngeal region.[141] Mask distention may also contribute to Vte in FMV.[142] O'Donnell et al. calculated in a manikin model that up to 18% of Vt could be distending the mask.[113] Tidal volumes above 10 ml/kg where also more common in infants ventilated with FM. We observed abdominal movements after video reviews in 3/23 infants in the FMV

group. These 3 infants had abnormally high Vte (range 17-21 ml/kg) suggesting that air entering and exiting the esophagus and stomach could contribute Vte, adding to the dead space. We speculate that this phenomenon could be clinically relevant, particularly in infants with airway obstruction or low lung compliance. Ventilation with LMA provides the same direct access to the lower airways as in ventilation with an ETT and could establish functional residual capacity (FRC) earlier despite lower Vte.

5.6 Too much too soon or too little too late: the importance of managing airway obstructions

Routine airway suctioning may be harmful and was recently de-emphasized in in the second edition of HBB.[11] In 2016, our collaborator, Dr. C. Lubulwa reviewed 99 video-recorded resuscitations performed at Mulago National Referral Hospital in Kampala.[143] Routine suctioning was performed in 81% of infants prior to resuscitation. Detrimental suction practice affecting the start of ventilation was common, with only 13% of cases deemed appropriate. The median start time to ventilation in the delivery room was 163 s (IQR 141-202).

During training, the trial team highlighted critical aspects of the current guidelines, such as avoiding prolonged suction and emphasizing the HBB concept of the Golden Minute (i.e. start ventilation of the non-breathing baby within 60 seconds). Secondary data analysis from the respiratory function monitor and associated videos (paper III and unpublished data) show that routine suctioning was reduced to 56.6 % in the FMV group (table 5). We also found that complete or partial obstruction of the airways during resuscitation occurred in about a quarter of all cases, necessitating aggressive suctioning to remove mucous plugs from the airways. This puzzling finding seems unrelated to the meconium aspiration syndrome since infants recovered from the respiratory distress after removal of the plug. The focus of suction research has mainly been mainly on preemptive clearing of the airways.[144-147] NRPs seventh edition has suggested against routine suctioning, even of depressed infants to minimalize delay in ventilation. Chiruvolu et al. have monitored admissions to the

NICU prospectively after implementation of the guideline changes and noted a significant increase of admissions to the NICU for respiratory failure.[148] To our knowledge, the specific problem of airway obstruction during PPV has not been investigated. Removal of the mucous plugs with standard bulb syringes was successful in most cases (figure 16).

Figure 16. *Removal of the mucous plug with a standard bulb syringe. (Photo: Nicolas Pejovic, with kind permission from the mother.)*

However, deep suctioning of the trachea was necessary in 3/46 cases. Active suction systems are rarely available outside high-resource settings. An adaptation of the Laerdal Penguin, paired with a 3.0 standard ETT tube and digital (=finger) intubation, proved useful in those cases (Figure 17). Resuscitation with LMA did not always seem to solve this clinical problem. In the LMA group (paper III), 17.4 % of infants needed deep suctioning intervention.

Figure 17. *Laerdal Penguin suction device adapted for endotracheal suctioning. (Photo: Nicolas Pejovic)*

Airway plugs were not always removed, despite the suspicion of obstruction. Animal studies have suggested that glottic and hypoglottic adduction may also play a critical role in particular for PPV of the preterm <32 weeks in particular.[149] It remains unclear if this fetal physiological mechanism, involved in enhancing lung expansion and lung growth, plays a critical role during resuscitation, and if LMA could minimize this type of airway obstruction.

We know that a routine suction practice may delay the onset of ventilation. However, our clinical observation suggests that compromised ventilation due to critical airway obstruction during newborn resuscitation may be more common than previously

thought, at least in this population with its high proportion of depressed infants. A high frequency of obstetric delays, maternal dehydration and chorioamnionitis in our research setting are possible causes of this serious complication. Deep suctioning methods are easy to learn and do not require special equipment. Although neonatal suction-practice has been an area of controversy for years, it may be worthwhile to assess its prevalence and exploring further the causes of postnatal airway obstruction in low-resource settings.

5.7 Methodological considerations and biases

5.7.1 The manikin study

Only a limited number of pediatric LMA studies had been conducted prior to our trials.[120] [121] The design of the manikin study (paper I) had certain limitations. First, the number of participants was limited. We conducted the pilot trial in the labor ward theatre and trained only the staff attached to this unit. Preclinical manikin studies can be regarded as equivalent to phase 1 in-vitro studies in pharmacological trials. The participants found insertion maneuvers for the LMA very easy, yet the model could never offer the size and anatomical variations or the wide size range from term to preterm infants. Health workers in the labor units had no previous experience of LMA. It would have been unethical to set up a clinical trial directly without knowledge of performance on a manikin and acceptability of the device. Despite obvious limitations, the findings served as a useful stepping-stone as we planned the clinical trials.

5.7.2 The clinical trials

Randomized controlled trials (RCTs) are designed to evaluate the causal relationships of a medical treatment strategy. A well-designed randomization method is paramount in establishing causation and to minimize any bias. Blinding was not possible as in most non-drug trials. Thus, bias from potential differential care of respective study arm could not be eliminated. An unmasked trial, however, offers the advantage of safety and effectiveness analysis in a real-world situation. We performed intention to treat (ITT) analyses in paper II and III. An option to switch to the alternative device

in the case of PPV failure after 3 min was part of the study design for ethical reasons. This short "wash-out" period with the intended device, challenged a true measurement of the effect of treatment. A per protocol (PP) analysis is likely to have biased the results, since the most depressed children may have shifted to the other arm in a differential manner.

We considered the calculation of the sample size for this task-shifting trial (paper II) appropriate, since it emphasized the safety aspects. The calculation for paper III was based on evidence-based assumptions from our own anecdotal observations and available manikin data. In hindsight, the small sample proved to be a problem in both studies. Important secondary outcomes, such has heart response and ventilation time (paper III) were not statistically significant. The wide confidence intervals could have generated Type I errors. The design of the NeoSupra trial is based on the pragmatic assumption that only a large reduction of adverse outcomes (25%) would justify the implementation of a radically different and more expensive resuscitation method. Setting up prospective randomized controlled trials in resource constrained settings presents particular methodological challenges. We used Cochrane Collaboration assessment tools (table 7) to help us identify design flaws and possible biases in the preparation of the trial protocol (paper III, annex).[150] The tool for assessing the risk of bias in randomized trials covers 6 domains of bias: performance bias, detection bias, attrition bias, selection bias, reporting bias, and other bias.

Table 7. *Risk of bias in paper II-III and Annex (NeoSupra trial)*

	Paper II	**Paper III**	**Annex**
Random sequence generation	Low risk	High risk	Low risk
Allocation concealment	Low risk	Low risk	Low risk
Blinding	High risk	High risk	High risk
Incomplete outcome data	Low risk	High risk	High risk
Selective reporting	High risk	High risk	Low risk
Other bias	High risk	High risk	?

5.7.3 Performance bias

Performance bias may occur due to the study team's awareness of the allocation of the participant. Health workers in the delivery room where not masked to the

intervention. The belief that the LMA was a life-saving device, could have led to some unwarranted switches in device. However, the use of LMA in the case of PPV failure with FM would have been likely in real clinical situations, limiting the impact of this bias in the primary outcome analysis.

5.7.4 Detection bias

A systematic difference in how outcomes are determined between study arms is referred to as detection bias. In paper III, we have reasons to believe that tidal volume calculated from the respiratory function monitor may have overestimated the Vte in the FMV group (Chapter 5.5).

5.7.5 Attrition bias

Attrition bias is the uneven loss of participants between study arms, but it seems not to have affected our trials. The primary outcomes of paper II and III were collected at the time of intervention. In the NeoSupra trial, significant efforts were made to keep the loss to follow-up < 5%

5.7.6 Selection bias

Selection bias is caused by improper randomization and introduces a systematic difference between study arms or populations. This type of bias is difficult to measure and adjust for. The limitation of the chosen randomization processes has been previously discussed. In paper III, participants were only recruited when a study-doctor was on duty, increasing the risk of a selection bias. The external validity of the trial may also be challenged, since the population in this large referral hospital is probably going to be more severely affected than in a lower health care center. Only a large multi-center trial could mitigate this effect. In the case of severely ill mothers suffering from conditions such as eclampsia, sepsis or uterine rupture developing, the oral consent requirement could lead to a selection of a *less* critically-ill cohort.

5.7.7 Reporting bias

Reporting bias occurs when selected outcomes from clinical trials are chosen for publication. Selective reporting was mitigated by prior publication of the outcomes (paper II-III) in *clinicaltrials.gov*. In paper III, we also chose to report rescue

suctioning outcomes because of the high occurrence of airway obstruction, which had not been predicted in the design of the trial.

5.7.8 Information bias

Improper data collection techniques can lead to information bias. The team maximized efforts to assure the quality of the data collection. Video review could complete missing data from research assistants in timing the resuscitation intervention. We performed dry runs of the data collection before recruitment started to improve the methodology of data collection. In paper III and in the NeoSupra trial, data managers used double data input. We performed an extensive data cleaning process before data analysis in paper III because of artefacts generating implausible data in ~10% of the recorded breaths.

The RAs assessed subjectively the Apgar score. The scoring can be altered by several factors during resuscitation and reliability has not been studied.[66] Stopwatches were used to record time from delivery to table, but double control from the RA supervisors showed that this data was often unreliable, a particular parameter that could not be corrected by video review.

5.7.9 Other biases

The Hawthorn effect is controversial and said to occur when participants or researchers modify their behavior by their awareness of being observed.[151] Interaction between the midwives and the asphyxiated infants was monitored by video and research assistants. Feedback was given to the staff for ethical reasons where serious deviations from guidelines were observed. The impact of the Hawthorn effect and internal validity of the studies could have been estimated using qualitative methods. A separate qualitative study with interviews of the focus group discussing the midwife's perception of their work and training is underway, which could help us understand behavioral aspects. An informal review of historical outcome data from the hospital ledgers seems to imply a positive impact on mortality rates that could be affecting both study arms.

5.7.10 A trial effect?

We cannot exclude that a "trial effect" was inadvertently introduced that would be systematically beneficial for all participants during implementation of the trials. Guidelines were more likely to be followed, new equipment was introduced in the delivery room, careful recycling of the resuscitation devices improved hygiene, and clinical feedback was given to the health workers. Participation in a trial is likely to be advantageous regardless of the study arm, but the evidence from the review of 17 RCTs was inconclusive.[152] We cannot exclude the unintended introduction of the trial effect that could affect the external validity of the results.

5.8 Emergency research ethics in vulnerable populations

The work presented in this thesis is the result of a collaborative of a partnership involving the host country. It seemed most relevant to conduct the trials in one of the country's large national referral hospitals because of the high number of participants required in the trial and the relatively low proportion of infants affected by birth asphyxia. The *Ethics of Research Related to Healthcare in Developing Countries* report from the Nuffield Council on Bioethics presents an ethical framework based on "4 sound principles of duty – the duty to alleviate suffering, to show respect for human beings, to be sensitive to cultural differences, and not to exploit the vulnerable.[153] The problem of informed consent in an emergency involving a care-taker in labor is particularly challenging.[154] The Declaration of Helsinki mentions a possibility of using deferred consent in a potentially life-threatening situation, when time constraints do not allow ordinary prospective consent; such trials remain controversial.[155] Unifying guidelines for emergency medicine research are still missing, but a review of the current literature offered a basis for discussion with the MREC preparing for the trials.[154-163] Extensive discussions with clinical experts and members of the ethical board were necessary to find a way of obtaining consent without delaying intervention. Deferred consent was approved for the first pilot trial (paper II), since an experienced anesthetist or neonatologist would supervise all interventions. A 2-tiered procedure for consent was implemented for the NeoSupra trial, including paper III, because of the size of the trial and the risks involved in

unsupervised resuscitation. This model had been applied in a similar trial in the hospital.[117] Free medical care was not a motivation for participation, but caretakers received a small travel compensation for follow-up visits. We faced unexpected difficulties when caretakers had to be approached in cases of a very early neonatal death. Research assistants were initially reluctant to increase the distress of caretakers with the deferred consent information. The inclusion of these cases in the NeoSupra trial (Annex) was crucial, since mortality was a primary endpoint. A deferred consent process with proper supervision from the trial team was successfully implemented after feedback from the research assistants. Caretakers in this situation are particularly vulnerable, and there are reasons to believe that waiver of consent could have been more appropriate. The 2-tiered process was labor-intensive and involved the presence of a dedicated research assistant 24/7. There are concerns that this cost-prohibitive method could potentially delay critical clinical investigations. Indeed, emergency medicine trials have become less frequent with current legislations creating barriers for potentially life-saving studies.[164 165] A solution to this situation would be to involve community leaders and stakeholders in the design of ethical design of high-risk trials. Such a method could provide a deeper understanding of local cultural contexts, and ultimately benefit both the participants and the trial.[166] A detailed discussion of this approach is beyond the purview of this thesis. Our studies, however, imply that much effort is still needed to improve current guidelines for ethically challenging neonatal resuscitation research.

6. Conclusions

- The LMA was more effective in establishing PPV in the manikin and user satisfaction was higher.
- LMA was more effective than FM in reducing time to spontaneous breathing.
- LMA was associated with faster HR recovery compared to FM in newborns with bradycardia.
- Mask leak and tidal volume in LMA was similar to FMV
- LMA seems to be a safe and effective device for newborn resuscitation in low-resource settings.

7. Implications and future perspectives

7.1 Implications for policy

The time has come to take further steps that will enhance newborn resuscitation globally. According to the current guidelines, LMAs should be used as an alternative airway if ETT is unavailable or unsuccessful. FMV, even under optimal conditions, will never solve the problem afflicting hundreds of thousands of asphyxiated infants in need of advanced airway management. Non-doctor staff, in particular in large referral facilities, needs to be trained to master enhanced resuscitation skills, including LMA ventilation. Current evidence and existing guidelines should prompt the WHO to consider adding the LMA to the list of priority medical devices for essential reproductive, maternal, newborn and child health. Stakeholders and ministries of health will also need cost-analysis data as they target large-scale implementation. Single-use and reusable LMAs remain at this time cost-prohibitive in resource-limited contexts. The LMA used in this study retails at ~12 $. Our data could contribute to the development of a low-cost reusable LMA for the global market. Preterm infants are notoriously challenging to ventilate with face-mask, and dedicated LMAs for infants of <1500g are warranted. A standardized curriculum that includes a low-cost manikin would be useful when implementing LMAs at secondary and tertiary levels.

7.2 Implications for future research

The combination of dry-electrode ECG, respiratory function monitor and HD video seems to be a winning combination in this type of investigation. We need to understand how different LMA designs may impact the resuscitation performance on preterm and term infants. Different manikin designs also need to be evaluated. The need for aggressive suctioning after failed PPV due to tracheal obstruction requires further investigation. Cross-sectional prevalence studies in various settings, combined with the analysis of the viscoelastic and microbiological properties of the tracheal

plugs would be of great importance for our understanding the pathophysiological mechanisms of this under-reported condition.

Finally, will the superior ventilation performance of the LMA also decrease neonatal mortality and neurological disability? Real progress has to be made if we are to reach the Sustainable Development Goal number 3 (SDG-3) of a global neonatal mortality rate of <12 in 1,000 live births by 2030. We have completed the NeoSupra trial in August 2019; the results should help define best practice advice for future guidelines.

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9. Errata

Page	**Now reads**	***Was***
Page 11	**Paper III:** Pejovic NJ, Cavallin F, Mpamize A, Lubulwa C, Myrnerts Höök S, Byamugisha J, Nankunda J, Tylleskär T, Trevisanuto D	**Paper III:** Nicolas NJ, Cavallin F, Mpamize A, Lubulwa C, Myrnerts Höök S, Byamugisha J, Nankunda J, Tylleskär T, Trevisanuto D

Paper I

ACTA PÆDIATRICA
NURTURING THE CHILD

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REGULAR ARTICLE

Pilot manikin study showed that a supraglottic airway device improved simulated neonatal ventilation in a low-resource setting

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ABSTRACT

Aim: We compared the performance of personnel in a low-resource setting when they used the I-gel cuffless neonatal laryngeal mask or a face mask on a neonatal airway management manikin.

Methods: At Mulago Hospital, Uganda, 25 doctors, nurses and midwives involved in neonatal resuscitation were given brief training with the I-gel and face mask. Then, every participant was observed positioning both devices on three consecutive occasions. The success rate and insertion times leading to effective positive pressure ventilation (PPV) were recorded. Participants rated the perceived efficiency of the devices using a five-point Likert scale.

Results: The I-gel achieved a 100% success rate on all three occasions, but the face mask was significantly less effective in achieving effective PPV and the failure rates at the first, second and third attempts were 28%, 8% and 20%, respectively. The perceived efficiency of the devices was significantly superior for the I-gel (4.7 ± 0.4) than the face mask (3.3 ± 0.8).

Conclusion: The I-gel was more effective than the face mask in establishing PPV in the manikin, and user satisfaction was higher. These encouraging manikin data could be a stepping stone for clinical research on the use of the I-gel for neonatal resuscitation in low-resource settings.

INTRODUCTION

Annually, 136 million babies are born worldwide. Approximately one million die each year due to intrapartum-related events, 96% of them in low- and middle-income countries (1–3). Successful resuscitation could prevent a large proportion of these deaths and improve the outcomes of neonates surviving asphyxia (3,4). Therefore, all birth attendants, including physicians, midwives and nurses, should have the knowledge and skills required to perform neonatal resuscitation (5). Providing effective positive pressure ventilation (PPV) is the single most important component of successful neonatal resuscitation (5). Ventilation is routinely initiated with face mask ventilation (FMV) followed by endotracheal intubation (ETT) in cases of FMV failure or the need for prolonged ventilatory support. Both these techniques may be difficult to perform, resulting in failure of effective resuscitation. Important air leakages and airway blockage have been reported during FMV. Skilled staff are required when ETT is performed (5). The laryngeal mask airway (LMA) may be considered during resuscitation as an alternative to FMV or ETT for PPV in newborns weighing more than 2000 g or delivered around, or after, 34 weeks of gestation (5). Several publications including a Cochrane review have shown that LMA achieved effective PPV in most of the treated patients, with

Abbreviations
ETT, Endotracheal tube; FMV, Face mask ventilation; LMA, Laryngeal mask airway; PPV, Positive pressure ventilation.

Key notes

- This study compared the use of the I-gel cuffless neonatal laryngeal mask or a face mask on a neonatal airway management manikin in a low-resource setting.
- The I-gel was more effective in establishing positive pressure ventilation, and user satisfaction was higher among the 25 doctors, nurses and midwives who took part.
- These positive findings could encourage further clinical research on the use of this device in low-resource settings.

a range of 95–99% (6–9) and reduced the need for ETT (1,10). In all of the previous studies, a classic inflatable size 1 LMA was used. The I-gel (Intersurgical Ltd, Wokingham, Berkshire, UK) is a new model of supraglottic airway device that has been made available and is designed to provide an efficient seal to the larynx without an inflatable cuff. The risk for trauma is minimised (2), and insertion is easy with a low risk of tissue compression or dislodgement (11). All these characteristics make the I-gel a potentially very useful alternative to FMV and ETT, especially in settings where the staff's skills in performing PPV are low. No randomised trials had been performed to evaluate the I-gel uncuffed supraglottic airway device and compare it with the FMV for neonatal resuscitation. A first step before conducting a clinical study on the neonates was to evaluate a high-fidelity training programme that could be implemented in health-care facilities with limited resources in a low-resource setting.

The aim of this study was to compare the performance, namely the ease of insertion and time to establish effective PPV, of personnel involved in neonatal resuscitation with limited experience in airway management when using the I-gel and face mask in a neonatal airway management manikin. The effectiveness of the two devices, as perceived by the participants, was also evaluated.

METHODS

A Helping Babies Breathe refresher course was held at the Labour Ward Theatre, Department of Obstetrics and Gynaecology, at the Mulago National Referral and Teaching Hospital Kampala in December 2012. Two certified neonatologists, who were also Neonatal Resuscitation Program instructors (NP, DT), held the course, which consisted of a didactic review of the Helping Babies Breathe neonatal resuscitation flowchart and practical hands-on skill stations. The lessons and practical skill stations included topics on the first steps of neonatal resuscitation, including thermal losses prevention, airway management and stimulation, and the use of the face mask. An additional module for training on the use of the I-gel was added.

The I-gel is a relatively new single-use supraglottic airway device, and the size 1 device is designed for neonates weighting 2–5 kg (Fig. 1). It comprises a soft, gel-like, noninflatable cuff made of thermoplastic elastomer that fits anatomically against the perilaryngeal structures and a rigid bite-block that acts as a buccal stabiliser to reduce axial rotation and malpositioning (11,12).

To teach the use of both devices, the face mask and the I-gel, to health staff, we used a high-fidelity manikin model, the SimNewB Laerdal (Laerdal, Stavanger, Norway). It provides realistic airways and good feedback with chest rise when effective PPV is provided. The face mask used was the Laerdal neonatal resuscitator (Laerdal Medical, Stavanger, Norway). We included all 25 of the staff available on daytime duty on a particular week.

All participants had previously used the face mask on a manikin model as well as in clinical practice for neonatal resuscitation. However, all of them said it was the first time they had placed a supraglottic airway device, in particular an I-gel. After the course, participants were asked to ventilate the manikin with the I-gel and face mask, respectively. Each participant was then observed positioning and inserting each of the two devices on three consecutive occasions. The order, starting with the I-gel or face mask, was randomly assigned using closed envelopes. The success rate and time to establish full chest rise, namely the insertion time, was recorded by a single unblinded observer. If more than 30 seconds elapsed before the chest rise was noticed, a new attempt was carried out. A five-point Likert scale was used to evaluate the ease of application and insertion and ventilation perceived by the participants. The perceived effectiveness of respective devices was scored by each participant immediately after the performance: one for insufficient, two for sufficient, three for fair, four for good and five for excellent. To avoid a desirability bias, participants were only informed afterwards of their involvement in this comparative study.

Figure 1 The I-gel and the face mask used in the study.

A convenience sample of healthcare volunteers was studied, and no sample size calculation was performed. The individual staff members consented to participate.

Data were collated and statistically analysed using the statistical package STATISTICA, StatSoft version 6 (www.statsoft.com). Differences between the two devices were determined using the paired t-test and the unpaired t-test, respectively. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 25 healthcare providers, 12 doctors and 13 midwives and nurses, participated in the study. All 25 participants completed the study and obtained effective PPV with the manikin model (Table 1). The I-gel enabled them to reach effective PPV at the first attempt on all three consecutive occasions. These performances were

Table 1 Insertion success rate, mean time to successful ventilation, perceived ease of insertion and perceived effectiveness of ventilation with I-gel™ and FM

	I-gel™ (*N* = 25)	FM (*N* = 25)	p value
Success rate	n (%)	n (%)	
1st attempt	25 (100)	18 (72)	<0.001
2nd attempt	25 (100)	23 (92)	<0.001
3rd attempt	25 (100)	20 (80)	<0.001
Mean time to successful ventilation	Mean ± SD	Mean ± SD	
1st attempt (seconds)	6.2 ± 2.3	8.3 ± 4.7	0.18
2nd attempt (seconds)	5.2 ± 1.1	9.9 ± 14.1	0.68
3rd attempt (seconds)	4.5 ± 1.0	6.6 ± 5.9	0.38
Ease of application/ ventilation	Median ± SD (range)	Median ± SD (range)	
Score (one lowest, five highest)	4.7 ± 0.4 (1–5)	3.3 ± 0.8 (1–5)	<0.001

significantly better ($p < 0.001$) than those obtained with the face mask. In fact, the face mask only allowed an effective PPV on the first attempt in 18/25 (72%), 23/25 (92%) and 20/25 (80%) of the first, second and third occasions, respectively. The mean and standard deviation insertion times for the I-gel were not significantly different to the face mask on the first (6.2 ± 2.3 versus 8.3 ± 4.7 seconds, $p = 0.18$), second (5.2 ± 1.1 versus 9.9 ± 14.1 seconds, $p = 0.68$) and third (4.5 ± 1.0 versus 6.6 ± 5.9 seconds, $p = 0.38$) occasions. The effectiveness score expressed by the participants for the I-gel on a five-point Likert scale was 4.7 ± 0.4, compared with 3.3 ± 0.8 for the face mask ($p < 0.001$).

DISCUSSION

This manikin study was performed among birth attendants in Uganda immediately after a training course of both face mask and supraglottic airway device ventilation skills. The 25 participants obtained better PPV with the I-gel than the face mask and found the I-gel much easier to use.

Our results demonstrate that both skilled and unskilled participants could rapidly learn to ventilate the manikin with the uncuffed supraglottic airway device. All participants achieved effective PPV on the manikin on all attempts. Furthermore, PPV could be established more rapidly, even if this difference was not statistically significant. Several participants failed to establish PPV within 30 seconds with the face mask. These data confirm that it is indeed a challenge to establish an effective seal with a face mask and sustain good ventilation. It is important to note that all participants had prior clinical experience with the face mask, whereas it was the first time they inserted the I-gel device.

Furthermore, the participants found it easier to establish PPV with the I-gel compared to the face mask. The acceptability and satisfaction expressed by healthcare providers, especially in low-resource settings, is another important issue to consider. Our data are in agreement with a previous manikin study conducted in Kinshasa, Democratic Republic of Congo, where participants manifested a high degree of approval of neonatal resuscitation using a classic supraglottic airways device (13).

Both stillbirths and neonatal mortality are high in low-income countries (2,3). As intrapartum-related complications, previously labelled as birth asphyxia, are responsible for a large number of these deaths, programmes that aim to improve neonatal management at birth are crucial (3).

Antenatal care improvements and an increase in the proportion of births attended by skilled personnel are mandatory to decrease intrapartum-related complications (4,14). Bhutta and Black (3) have suggested that a strategy based on low-cost training materials and standardised training manuals and equipment such as manikins and resuscitation bags may help to reach this goal. However, the quality of educational interventions needs to be assessed in simulated as well as clinical settings.

As effective PPV is the most important intervention during neonatal resuscitation, educational efforts should mainly concentrate on this task and it is essential that all those involved in the care of newborn infants at birth are able to perform this procedure (5).

The 2015 International Guidelines for Neonatal Resuscitation state that a laryngeal mask may be considered during resuscitation as an alternative to a face mask for PPV among newborn infants weighing less than 2000 g or delivered around or after 34 weeks of gestation (5). In the setting of neonatal resuscitation, previous observational studies have showed that LMA allowed effective PPV in most of the patients that were treated, with a range of 95–99% (6–8). One quasi-randomised study showed that the LMA was more effective than face mask ventilation for neonates with an Apgar score of 2–5 at one minute after birth. The authors concluded that the LMA was safe, effective and easy to implement for the resuscitation of neonates with a gestational age of 34 or more weeks (10). A further study, conducted in a middle-income country, confirmed that the neonatal LMA Supreme (Teleflex Inc, Wayne, PA, USA) was more effective than a face mask in preventing endotracheal intubation in newborns with a gestational age of 34 weeks or more and, or, an expected birthweight of at least 1500 g needing PPV at birth (15). All these studies were conducted using a cuffed supraglottic airways device (6–10). The innovative design of the I-gel could simplify insertion and should be well suited for this task. A meta-analysis demonstrated that the LMA Supreme and the I-gel supraglottic airways device models were similarly successful and rapidly inserted during anaesthesia in adult patients (16).

While our study demonstrated that the use of the I-gel could be easily taught to local healthcare workers in low-income countries, it does have some limitations. It was a manikin study with only a small number of healthcare workers involved. The training was carried out *in situ* at the labour ward with limited time available. The knowledge retention over time was not assessed, nor was the ability to sustain PPV over a longer period of time. The skills acquired

using the I-gel on the manikin have not yet been applied in the delivery room. The insertion of the I-gel supraglottic airways device may be more difficult in a neonate than in a manikin. The comparison of the I-gel and face mask needs to be reproduced in a clinical setting. If it turns out that I-gel is superior to a face mask, the price issue must be addressed for it to become a real alternative in low-resource settings. It is a single-use device currently sold in the European Union for the equivalent of 12 U.S. dollars.

CONCLUSION

The use of the I-gel can easily be taught to healthcare workers in facilities in low-income countries within the framework of the Helping Babies Breathe curriculum. The neonatal I-gel was superior to the face mask in establishing effective PPV, and the healthcare workers felt it was easier to use than the face mask. These manikin data provide a useful stepping stone for future clinical research on neonatal resuscitation with a supraglottic airways device in low-resource settings.

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CONFLICT OF INTERESTS

None declared.

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Paper II

OPEN ACCESS

Neonatal resuscitation using a laryngeal mask airway: a randomised trial in Uganda

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ABSTRACT

Objective Mortality rates from birth asphyxia in low-income countries remain high. Face mask ventilation (FMV) performed by midwives is the usual method of resuscitating neonates in such settings but may not always be effective. The i-gel is a cuffless laryngeal mask airway (LMA) that could enhance neonatal resuscitation performance. We aimed to compare LMA and face mask (FM) during neonatal resuscitation in a low-resource setting.

Setting Mulago National Referral Hospital, Kampala, Uganda.

Design This prospective randomised clinical trial was conducted at the labour ward operating theatre. After a brief training on LMA and FM use, infants with a birth weight >2000 g and requiring positive pressure ventilation at birth were randomised to resuscitation by LMA or FM. Resuscitations were video recorded.

Main outcome measures Time to spontaneous breathing.

Results Forty-nine (24 in the LMA and 25 in the FM arm) out of 50 enrolled patients were analysed. Baseline characteristics were comparable between the two arms. Time to spontaneous breathing was shorter in LMA arm than in FM arm (mean 153 s (SD±59) vs 216 s (SD±92)). All resuscitations were effective in LMA arm, whereas 11 patients receiving FM were converted to LMA because response to FMV was unsatisfactory. There were no adverse effects.

Conclusion A cuffless LMA was more effective than FM in reducing time to spontaneous breathing. LMA seems to be safe and effective in clinical practice after a short training programme. Its potential benefits on long-term outcomes need to be assessed in a larger trial.

Clinical trial registry This trial was registered in https://clinicaltrials.gov, with registration number NCT02042118.

What is already known on this topic?

- Birth asphyxia contributes to almost 1 million neonatal deaths.
- Positive pressure ventilation is the most important component of successful neonatal resuscitation.
- Ventilation with face mask (FM) is a difficult skill to master, particularly in low-income settings.

What this study adds?

- A cuffless laryngeal mask airway (LMA) reduced time to spontaneous breathing compared with FM during newborn resuscitation in a low-resource setting.
- LMA is effective and easy to use after a short-term training programme even in the hands of inexperienced staff.

INTRODUCTION

Each year, intrapartum-related complications (birth asphyxia) result in 1.2 million stillbirths, 700 000 term newborn deaths and an estimated 1.2 million babies developing neonatal encephalopathy (previously called hypoxic ischaemic encephalopathy).[1 2] Of these, 96% occur in low-income and middle-income countries.[3 4] Successful resuscitation could prevent a large proportion of these deaths and improve the outcomes of neonates surviving asphyxia.[3 5 6] Therefore, all birth attendants, including physicians, midwives and nurses ought to have the knowledge and skills required to perform neonatal resuscitation.[7] Providing effective positive pressure ventilation (PPV) is the single most important component of successful neonatal resuscitation.[7] Ventilation is routinely initiated with face mask (FM) followed by endotracheal intubation in case of face mask ventilation (FMV) failure or need for prolonged ventilatory support. Endotracheal intubation is the most difficult skill to master in neonatal resuscitation and mostly properly performed only by experienced physicians.[8] Mask leakage, airway blockage and poor chest expansion have been reported during FMV.[9] The American Heart Association and the European Resuscitation Council Guidelines have proposed to use the laryngeal mask either as a primary device, replacing FM if ventilation is ineffective, or as an alternative to intubation during resuscitation of the late-preterm and term newborns (≥34 weeks gestation and/or birth weight >2000 g).[10] Several publications including a Cochrane review have shown that the laryngeal mask allowed effective PPV in most of the treated patients (range 95%–99%)[11–14] reducing the need for intubation.[15] In previous studies, a classic inflatable size 1 laryngeal mask was used.[11 12 15 16] The i-gel size 1 is a new model of cuffless laryngeal mask airway (LMA), also described as a supraglottic airway, that has recently been made available for newborns (2–5 kg). It is designed to provide an

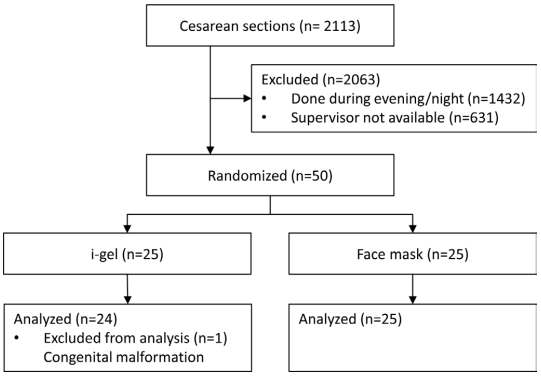

Figure 1 CONSORT flow diagram.

efficient seal to the larynx without an inflatable cuff. Positioning is easy with a low risk of tissue compression or dislodgement.[17] All these characteristics make the cuffless LMA a potentially useful alternative to FM and endotracheal intubation, especially in settings where the staff skills in performing PPV are insufficient.[15] In a previous manikin study conducted in a low-resource setting, we found that the LMA was more effective than FM in establishing PPV,[18] but there are no published randomised trials comparing the LMA with the FM during neonatal resuscitation.

The aim of the current trial was to determine if the LMA can reduce the time to spontaneous breathing of newborns needing PPV in a large delivery ward, where resuscitation is mainly performed by midwives. The safety of the intervention was determined by the assessment of clinical outcomes and side effects.

PATIENTS AND METHODS

Setting

This was a phase II, single-centre, prospective, open-label, randomised controlled trial (RCT) conducted at the Department of Obstetrics and Gynaecology, Mulago National Referral Hospital in Kampala, Uganda, where about 33 000 deliveries occur every year. Due to local organisational aspects, the trial was conducted at the operating theatre where 15–30 caesarean sections, most of them on emergency basis, are performed each day.

Inborn infants satisfying the following inclusion criteria were eligible to participate in the trial: gestational age >34 weeks by best obstetric estimate (last menstrual period or ultrasound scan), expected birth weight >2000 g, need for PPV at birth and written parental consent. Exclusion criteria included presence of major malformations.

Recruitment and implementation

Participants were recruited in the operating theatre among mothers awaiting caesarean section because of fetal distress. The bilingual consent form was given to mothers assessed by a doctor from the obstetric department, proficient in Luganda, the most common local language in the Kampala region. Recruitment took place only daytime on days when a supervisor available to oversee resuscitations (figure 1). This safety requirement delayed the completion of the study.

Training

Before the trial, all the staff involved in neonatal resuscitation participated in a Helping Babies Breathe (HBB) refresher course (version 1). All participants had previously attended at least one course on neonatal resuscitation. Two certified instructors in neonatal resuscitation held the course. It consisted in a review of the HBB action plan and practical hands-on skill stations. The training included simulation scenarios involving key procedures of the action plan (thermal loss prevention, stimulation, clinical assessment, airway management and so on) and the use of the FM (Laerdal silicon resuscitator, Laerdal Medical, Stavanger, Norway). The HBB course does not include chest compressions and medications. An additional module for training on the use of the i-gel (Intersurgical, Wokingham, Berkshire, UK) LMA was added. A high-fidelity model (SimNewB Laerdal manikin, Laerdal Medical) was used to train the staff in the use of both devices (LMA and FM). It provides realistic airways and good feedback with chest rise when effective PPV is provided. The staff learnt an insertion technique that is similar in the manikin compared with the newborn. A silicon lubricant facilitated the procedure (not needed in the newborn due to oral secretions). The LMA was placed with the outlet facing towards the chin of the baby with the head maintained in a neutral position. The chin was pressed down to open the mouth while the soft tip got inserted into the mouth towards the hard palate. The device was further inserted downward along the hard palate until the tip met a definite resistance. If the cuff was correctly located against the laryngeal inlet, PPV resulted in chest rise. FMV was taught according to the HBB curriculum. In case of failed FMV, the participants were instructed to apply following corrective measures before considering the alternative airway: reapplication of the mask, repositioning of the head and increase of the inspiratory pressure. The use of suction was de-emphasised. Twenty-eight participants (13 midwives or anaesthetist nurses and 15 physicians) were trained. A minimum of three successful LMA insertions and three FMV performances in the manikin were required of all participants before starting the trial. All staff participating in the study had received similar HBB neonatal resuscitation training prior to the course.

Intervention

All neonates were cared for in accordance with the updated Mulago Hospital neonatal resuscitation flow chart based on HBB (version 1). All resuscitations were performed by health staff under supervision of instructors who could provide corrective measures, if needed. The HBB principle of the Golden Minute was applied and included drying, stimulation and, if necessary, clearing the airways of the baby with a bulb suction device. Heart rate (HR) was assessed at 60, 90, 180 and 240 s. PPV with LMA or FM was initiated in case of apnoea and/or gasping and/or HR <100 bpm at 1 min of life. PPV was administered with a 240 mL silicon self-inflating bag with a pop-off valve limit at 35 cm H_2O (Laerdal Medical). Silicone, round-shaped FM (size 1, Laerdal Medical) and i-gel LMA (size 1) were available at each delivery (figure 2). Babies that failed on the assigned device (LMA or FM) were converted to the alternative device (LMA or FM). Failure was defined as poor HR response and/or lack of chest rise. Manual ventilation was initiated in room air at a frequency of 40–60 breaths per minute. Endotracheal intubation is not possible in this setting. All babies with 5 min Apgar score <5, respiratory distress, hypothermia (axillary temperature <36.0°C) or signs of encephalopathy were transferred to the neonatal special care unit.

Data collection

All resuscitations were recorded on audio-enabled video using a waterproof Lumix DMC-FT5 HD camera (Panasonic, Osaka,

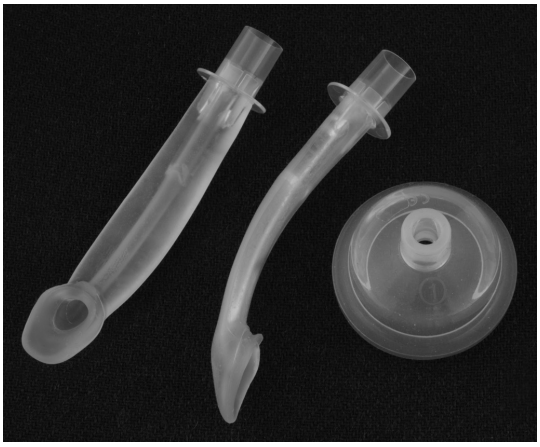

Figure 2 The i-gel and face mask.

Japan) attached to a mount on the resuscitation table. Recording started manually at time of birth and stopped at the end of the resuscitation procedure. The baby, the health providers' hands and the tablet for data recording were continuously filmed with narrow field of view. This allowed precise assessment of time to spontaneous breathing, assistance by supervisor and conversion to alternative device by trial arm. The HR of the patient was collected using the NeoTap app (www.Tap4Life.org), a newly developed mHealth software for Android and IOS mobile devices. HR was obtained by advanced users (NJP and CL) auscultating the heart and simultaneously tapping the screen for three beats. HR data at 30 and 60 s after birth are not possible with current pulse oximetry technology.

Three research assistants recorded perinatal data postoperatively in an Excel database (Microsoft Corp, Redmond, Washington). The video data were reviewed separately by two investigators. Non-matching data were reviewed by a third investigator.

Outcomes

Primary outcome was the time to spontaneous breathing defined as the sum of time elapsed from birth to initiating PPV and the ventilation time. Secondary outcomes were admission to neonatal unit in the first 48 hours of life, hypoxic ischaemic encephalopathy, death and adverse effects secondary to the procedure (vomiting, bleeding or laryngospasm). HR was added as an outcome because a non-invasive method was made available.

Sample size

In accordance with a previous study on this topic,[15] we expected a longer time to spontaneous breathing with FM than with LMA. Moreover, we estimated time to spontaneous breathing to be longer in our sample because of delays in delivery and difficulties in assessing fetal distress at Mulago Hospital. Time to spontaneous breathing was modelled with gamma distribution as right-skewed data of duration.[19] In accordance with local clinical observations and available information in a similar setting, we hypothesised a mean time to spontaneous breathing of 210 s (with shape parameter k 5.3) with FM and of 150 s (with shape parameter k 6.8) with LMA.[15] With a power of 0.80 and a type I error of 0.05, the sample size was estimated in 23 subjects per arm, for a total of 46 subjects.[20] This number was increased by 10% to cater for post hoc exclusions, thus we planned to enrol 50 subjects. This sample size was also considered appropriate for a task-shifting trial emphasising safety aspects when involving midwives for the first time in advanced airway management.

Random assignment

Each newborn was randomised at birth using a small opaque plastic container concealing 25 white and 25 black toothpicks. The colour of the randomly plucked toothpick determined if LMA or FM would be used. If the baby needed resuscitation, the toothpick would be broken and removed from the container. If not, it was put back into the container. This randomisation method was found appropriate for a low-resource context with limited space and power availability.

Statistical analysis

Categorical data were expressed as number and percentage and were compared between the two arms using Fisher's exact test. Birth weight was expressed as median and IQR and compared between the two arms using Mann-Whitney test. Duration data (time to spontaneous breathing, start of PPV and ventilation time) were modelled with gamma distribution, which is often used to model the time required to perform some procedures. In fact, the gamma distribution is bounded on the left at zero, thus excluding negative values (and negative duration data are impossible). The gamma distribution is also positively skewed, meaning that it has an extended tail to the right of the distribution. This allows a non-zero probability of very long time required to perform the procedure, even though the typical time to perform the procedure may not be very long. Observed duration data were summarised as mean and SD. The effect of the device (LMA and FM) on duration data was assessed using a gamma model. HR was recorded at different time points during the trial and was expressed as mean and SD. A linear mixed effect models was used to assess the effect of the device on HR, accounting for the longitudinal structure of the data. A p value less than 0.05 was considered statistically significant. Statistical analysis was performed using R V.3.2.2 software (R Foundation for Statistical Computing, Vienna, Austria).[21]

Ethical considerations

The protocol was approved by the Institutional Review Board of Mulago National Referral Hospital, the Uganda National Council of Science and Technology, the National Drug Authority and by the Regional Committee for Medical Research Ethics of Southern Norway, Section D in Norway.

The i-gel LMAs were purchased for the study without corporate sponsorship.

Written and oral information was obtained from the parent(s) on maternal admission, and a senior investigator was available to discuss any questions regarding the trial. Informed written consent was signed by a parent or caregiver before admission to the operating room.

RESULTS

Fifty patients (25 LMA and 25 FM) were enrolled in 2014 from April 24 to August 5. The trial was ended on August 7 after the last completed follow-up. One patient in the LMA arm was excluded after resuscitation due to congenital cardiac malformation, thus the final sample included 49 patients (figure 1). All patients were delivered by emergency caesarean section. Maternal and neonatal characteristics were comparable in the

Table 1 Baseline maternal and neonatal characteristics by trial arm

	LMA (intervention) n=24 n (%)	Face mask (comparator) n=25 n (%)	p Value
Caesarean section	24 (100)	25 (100)	–
Primiparous	9 (38)	9 (36)	0.99
(Pre-) Eclampsia	0	3 (12)	0.23
Placenta abruption	0	2 (8)	0.49
Oligohydramnios	2 (8)	1 (4)	0.61
Foul smell	3 (13)	4 (16)	0.99
Meconium stained	10 (42)	13 (52)	0.57
Male gender	13 (54)	13 (52)	0.99
	Median (IQR)	Median (IQR)	
Gestational age (weeks)	Not available	Not available	–
Birth weight (gram)	3100 (2962–3478)	2700 (2520–3400)	0.13
Apgar score 1 min	4 (3–5)	4 (3–5)	0.73
Apgar score 5 min	8 (7–9)	7 (6–9)	0.26
Apgar score 10 min	10 (9-10)	9 (8–10)	0.17

two arms (table 1). Accurate gestational age was unavailable for most patients.

Forty-two resuscitations (86%) were performed by midwives (21 in FM group and 21 in LMA group), while the remaining 7 (14%) by physicians (three in FM group and four in LMA group). Information on the procedure is shown in table 2. Overall, PPV started after a mean of 64 s (60 s in LMA arm and 68 s in FM arm; p=0.26). Total ventilation time was shorter in LMA arm than in FM arm (mean 93 s vs 140 s, p=0.02). Assistance from the supervising physician was required in nine procedures (three in LMA arm and six in FM arm; p=0.46). Incorrect FM position (n=4) had an impact on PPV prior to repositioning. Misplaced LMA (n=1) that could lead to potential side effect was verbally corrected in one instance before insertion. All procedures were effective in the LMA arm, whereas 11 patients receiving FM were converted to LMA after 150 s because response to FMV was deemed unsatisfactory by the supervisor (p=0.0002) because of poor HR response and/or lack of chest rise.

Mean time to spontaneous breathing was 153 s (SD 59) with LMA and 216 s (SD 92) with FM (p=0.005; table 3). The model estimated a mean reduction of 31% (95% CI 11% to 44%) in time to spontaneous breathing with LMA. The outcome in the first 48 hours of life was similar in the two arms (table 3). Thirteen patients needed admission to the neonatal unit (five in LMA arm and eight in FM arm), two patients in FM arm suffered hypoxic ischaemic encephalopathy and one patient in FM arm died within the first 48 hours of life. There were no adverse effects of the LMA such as laryngospasm, bleeding or vomiting.

HR increased during the first 240 s of life (p<0.0001) and was higher in LMA arm than in FM arm (p=0.0006), but the rate of increase was similar in the two arms (p=0.48) (figure 3 and online supplementary table 1). The proportion of patients with HR <100 bpm decreased in both arms from about 80% at 30 s after birth to 4% at 240 s after birth.

DISCUSSION

The most relevant results of this small phase II trial include (A) time to spontaneous breathing and total ventilation time were significantly shorter in the LMA arm than in FM arm; (B) almost half (44%) of the neonates who did not respond to FMV were successfully rescued with the LMA; (C) use of neonatal LMA was safe, even in the hands of inexperienced health staff.

A few observational studies and RCTs have evaluated the use of cuffed laryngeal masks during neonatal resuscitation and have unanimously concluded that laryngeal mask allowed effective PPV in most of the treated patients (range 95%–99%).[11 13 14] One quasirandomised study showed that successful resuscitation with the laryngeal mask was significantly higher, and the total ventilation time with the laryngeal mask was significantly shorter than with FMV. The authors concluded: 'the laryngeal mask is safe, effective and easy to implement for the resuscitation of neonates with a gestational age of 34 or more weeks'.[15] Another recent study from Vietnam confirmed that a new neonatal laryngeal mask (Supreme-LMA) was more effective than FM in preventing endotracheal intubation in newborns needing PPV at birth.[22] All these studies were conducted by using a cuffed laryngeal mask.[23] Our findings add that a cuffless supraglottic airway is also more effective than an FM in achieving a rapid recovery of neonates in need of PPV at birth. The innovative design of the LMA simplifies positioning and should be well suited for clinical settings lacking staff experienced in airway management.

Training of staff involved in neonatal resuscitation has been identified as a crucial factor in reducing neonatal mortality. The

Table 2 Time to start of ventilation, ventilation time, assistance by supervisor and conversion to alternative device by trial arm

	LMA (intervention) n=24 Mean (SD)	Face mask (comparator) n=25 Mean (SD)	p Value	Effect of the intervention Mean ratio (95% CI)
Start of PPV (s)	60 (11)	68 (36)	0.26	0.88 (0.70 to 1.10)
Ventilation time (s)	93 (52)	140 (90)	0.02	0.67 (0.47 to 0.93)
	n (%)	n (%)		OR (95% CI)
Assistance from the supervising physician	3 (13)	6 (24)	0.46	0.46 (0.07 to 2.52)
Conversion to alternative device	0	11 (44)	0.0002	0.00 (0.00 to 0.29)

PPV, positive pressure ventilation.

Table 3 Primary and secondary outcomes by trial arm

	LMA (intervention) n=24 mean (SD) range	Face mask (comparator) n=25 mean (SD) range	p Value	Effect of the intervention Mean ratio (95% CI)
Primary outcome			0.005	0.70 (0.56 to 0.89)
Time to spontaneous breathing (s)	153 (59) 45–300	216 (92) 65–395		
	n (%)	n (%)		OR (95% CI)
Secondary outcomes				
Admission to neonatal unit (first 48 hours)	5 (21)	8 (32)	0.52	0.56 (0.12 to 2.42)
Neonatal encephalopathy	0	2 (8)	0.49	0.00 (0.00 to 5.51)
Death within 48 hours	0	1 (4)	0.99	0.00 (0.00 to 40.63)
Adverse effects (vomiting, bleeding or laryngospasm)	0	0	0.99	Not applicable

LMA, laryngeal mask airway.

meta-analysis of existing studies suggests that neonatal resuscitation training in facilities is associated with a 30% reduction in intrapartum-related neonatal mortality.[24] Low-intensity high-frequency training programme are essential for maintaining skills and proper clinical practice.[6 25 26] FMV is an essential part of this training, but reaching and maintaining adequate performance represent a continuous challenge for both experienced and inexperienced caregivers.[25]

Task-shifting the use of supraglottic airways to non-doctor or inexperienced health staff in rural areas could be one way to improve the current situation. In agreement with previous studies,[15 22] our data suggest that the learning curve to reach adequate proficiency in the use of supraglottic airways is steep. Ventilation with LMA can also be performed using one hand only. This may be crucial in remote setting where birth attendants typically work alone and may need to resuscitate the baby by the mother.

Video-recording allowed precise and objective assessment of the primary outcome. The camera was manually operated by the supervisor. This led to a minor disturbance around the resuscitation table. Once started, the camera did not seem to interfere with clinical activity. The overall impression was that video-recording was well accepted by local staff. The potential use of the video for feedback and training was beyond the scope of this trial but is appealing and as has been used mostly in high-income settings.[9 27]

There are some limitations in this RCT. First, it was a phase II trial, so only a limited number of patients were included. Second, it was open-label as no masking or blinding is possible in this type of trial. Third, health caregivers responsible for resuscitation were under supervision of a trained person potentially influencing the procedure, but this was similar for both arms.

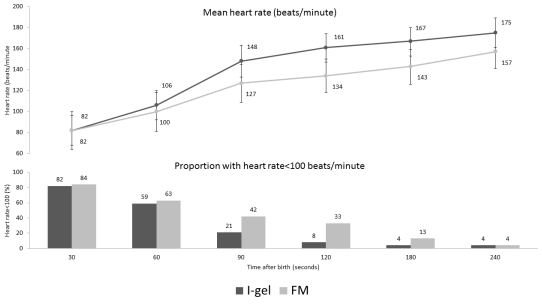

Figure 3 Mean heart rate (bpm).

Additional data such as accurate gestational age, signs of fetal distress, blood gases and oxygen saturation were not available in this low-income setting. HR was instead obtained with an mHealth tool (www.tap4life.org).

Earlier studies have assessed cuffed laryngeal masks during neonatal resuscitation in high-income and middle-income settings with experienced staff. This trial assesses the efficacy and safety of a cuffless supraglottic airway in the hands of staff inexperienced in administrating PPV at birth after a short training programme in a low resource setting.

CONCLUSION

Mastering PPV during newborn resuscitation is a difficult skill. A cuffless LMA reduced the time to spontaneous breathing during newborn resuscitation compared with FM. The LMA seems to be safe and effective in a low-income setting after a short training programme.

Contributors NJP had the idea and was responsible for conception and design, outcome assessment, acquisition of data, data analysis and interpretation, and drafted the manuscript. DT was responsible for trial design, outcome assessment, data analysis and manuscript writing. CL was responsible for on-site trial planning, data gathering, data analysis and critically revising the manuscript for important intellectual content. JN was responsible for on-site trial planning, data analysis, and critically revising the manuscript for important intellectual content. SMH was responsible for outcome assessment, acquisition of data, data analysis and interpretation, and critically revising the manuscript for important intellectual content. JB was responsible for on-site trial planning, data analysis and interpretation, and critically revising the manuscript for important intellectual content. FC was responsible for statistical analysis and interpretation, and critically revising the manuscript for important intellectual content. TT was responsible for conception and design, outcome assessment, data analysis and interpretation, and critically revising the manuscript for important intellectual content.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Review Board (IRB) of Mulago National Referral Hospital, the Uganda National Council of Science and Technology, the National Drug Authority and by the Regional Committee for Medical and Health Research Ethics (REK VEST) in Norway.

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Data sharing statement All authors of this article accept to share the complete dataset of this article. The data will be made available for all reasonable requests by online access with a password.

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Annex

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Trials

STUDY PROTOCOL Open Access

Neonatal resuscitation using a supraglottic airway device for improved mortality and morbidity outcomes in a low-income country: study protocol for a randomized trial

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Abstract

Background: Intrapartum-related death is the third leading cause of under-5 mortality. Effective ventilation during neonatal resuscitation has the potential to reduce 40% of these deaths. Face-mask ventilation performed by midwives is globally the most common method of resuscitating neonates. It requires considerable operator skills and continuous training because of its complexity. The i-gel® is a cuffless supraglottic airway which is easy to insert and provides an efficient seal that prevents air leakage; it has the potential to enhance performance in neonatal resuscitation. A pilot study in Uganda demonstrated that midwives could safely resuscitate newborns with the i-gel® after a short training session. The aim of the present trial is to investigate whether the use of a cuffless supraglottic airway device compared with face-mask ventilation during neonatal resuscitation can reduce mortality and morbidity in asphyxiated neonates.

Methods: A randomized phase III open-label superiority controlled clinical trial will be conducted at Mulago Hospital, Kampala, Uganda, in asphyxiated neonates in the delivery units. Prior to the intervention, health staff performing resuscitation will receive training in accordance with the Helping Babies Breathe curriculum with a special module for training on supraglottic airway insertion. A total of 1150 to 1240 babies (depending on cluster size) that need positive pressure ventilation and that have an expected gestational age of more than 34 weeks and an expected birth weight of more than 2000 g will be ventilated by daily unmasked randomization with a supraglottic airway device (i-gel®) (intervention group) or with a face mask (control group). The primary outcome will be a composite outcome of 7-day mortality and admission to neonatal intensive care unit (NICU) with neonatal encephalopathy.

(Continued on next page)

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Discussion: Although indications for the beneficial effect of a supraglottic airway device in the context of neonatal resuscitation exist, so far no large studies powered to assess mortality and morbidity have been carried out. We hypothesize that effective ventilation will be easier to achieve with a supraglottic airway device than with a face mask, decreasing early neonatal mortality and brain injury from neonatal encephalopathy. The findings of this trial will be important for low and middle-resource settings where the majority of intrapartum-related events occur.

Trial registration: ClinicalTrials.gov. Identifier: NCT03133572. Registered April 28, 2017.

Keywords: Global health, Low-income country, Laryngeal mask, Supraglottic airway device, Positive pressure ventilation, Newborn infant, Resuscitation, Neonatal mortality, Asphyxia, Asphyxia neonatorum, Intrapartum-related complications

Background

Problem statement

Since 2015, after Millennium Development Goal number 4 (MDG-4), of globally reducing by two thirds the under-5 (years of age) mortality, was summarized, it has become evident that neonatal mortality does not decrease at the same pace as post-neonatal mortality [1].

Of the 140 million babies born in the world annually, 7–9 million will need resuscitation at birth. The latest estimates are that 662,000 deaths annually are caused by intrapartum-related events, commonly referred to as birth asphyxia, which is the third leading cause of under-5 mortality globally [2].

Key health indicators from Uganda in 2017 show that child (under-5) mortality decreased from 175 out of 1000 in 1990 to 53 out of 1000 in 2016 [3]. The rate of neonatal mortality, however, is estimated at 27 out of 1000 and remains unchanged despite the national roll-out of programs such as Helping Baby Breathe (HBB) [3, 4], a basic neonatal resuscitation curriculum for resource-limited settings aiming at improving skilled attendance at birth [5]. HBB implementation trials have demonstrated a reduction in fresh stillbirths and first-day neonatal mortality. However, recent studies in India, Kenya, and Nepal assessing long-term outcomes showed no change in overall 28-day neonatal mortality or perinatal mortality [6, 7].

Sustainable Development Goal number 3 (SDG-3) re-emphasizes the need of accelerating the reduction of neonatal mortality; each country should aim for a neonatal mortality below 12 out of 1000 live births by 2030. Achieving this goal will be possible only if we improve existing neonatal resuscitation programs [8]. All birth attendants, including physicians, midwives, and nurses, should have the knowledge and skills required to perform effective neonatal resuscitation [9]. Innovative tools that can strengthen existing strategies will have to be rapidly implemented if we are to reach the 12 out of 1000 target of neonatal death by 2030.

Rationale

Providing positive pressure ventilation (PPV) is the single most important component of successful neonatal resuscitation [8, 9]. Yet the mortality of newborns needing face mask (FM) ventilation was as high as 10% in Tanzania [10].

Effective ventilation during neonatal resuscitation has the potential to reduce 40% of intrapartum-related deaths [11]. However, the delivery of proper tidal volume is a difficult technique to master. Mask leakage, airway blockage, and poor chest expansion have been reported during FM ventilation [12–14].

Ventilation is routinely initiated with FM followed by endotracheal intubation in case of FM ventilation failure or need for prolonged ventilatory support. Endotracheal intubation is the most difficult skill to master in neonatal resuscitation and performed only by experienced physicians [15]. The use of endotracheal tube (ETT) is not included in resuscitation guidelines aimed at low-resource settings [16].

The American Heart Association and the European Resuscitation Council guidelines have proposed the use of the laryngeal mask airway (LMA) to replace FM if ventilation is ineffective or as an alternative to ETT during resuscitation of the late-preterm and term infants (at least 34 weeks' gestation or birth weight of more than 2000 g or both) if intubation is unsuccessful [17].

Several publications, including a recent Cochrane review [18, 19], have shown that the LMA allowed effective PPV in most of the treated patients (range of 95–99%) [20–24], reducing the need for intubation [25, 26]. In previous studies, an inflatable size 1 laryngeal mask was used [21, 23–27].

The i-gel® (Intersurgical Ltd., Wokingham, Berkshire, UK) size 1 is a new model of cuffless supraglottic airway device that has recently been made available for newborns (2–5 kg). It is designed to provide an efficient seal to the larynx without the inflatable cuff used in the traditional LMA. Positioning is easy with a low risk of tissue

compression or dislodgement [28–30]. All of these characteristics make the i-gel® a potentially useful alternative to FM and ETT, especially in settings where the staff skills in performing PPV are insufficient [25–27]. A prospective observational study of 50 children demonstrated a success ratio of 100% for the insertion of the i-gel®. All devices were inserted on the first attempt. The study showed very few complications and concluded that it seems to be a safe and efficient device for pediatric airway management [31].

Task shifting the use of a cuffless supraglottic airway device to non-doctor or inexperienced health staff in resource-limited settings could be one way to improve outcome following newborn resuscitation. A manikin study in Uganda demonstrated that midwives could easily insert a cuffless supraglottic airway after brief on-the-job training: the i-gel® was also more effective than FM in establishing PPV in the manikin. In 2015, a phase II randomized controlled trial (RCT) on the same site demonstrated that midwives could effectively and safely perform resuscitation in neonates with the i-gel® [32, 33].

The effectiveness and safety of a supraglottic airway device compared with FM, as the primary interface for newborn resuscitation, are still identified as important knowledge gaps. The critical outcomes of mortality and indicators of brain damage also need to be assessed [34]. The proposed trial will follow the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [35] and provide evidence to determine whether use of a supraglottic airway device translates into better clinical outcomes and thus can be considered part of future guidelines for neonatal resuscitation in resource-limited settings (Additional file 1). The aim of the present trial will be to compare the effectiveness of two interfaces (i-gel® versus FM) for administering PPV at birth in terms of 7-day mortality and neonatal encephalopathy.

Methods/design

Trial design

A randomized phase III open-label superiority controlled clinical trial will be conducted in neonates needing PPV at birth with two parallel groups (1:1 ratio): resuscitation with a supraglottic airway device (i-gel®) compared to FM (standard of care).

Setting

This trial will be conducted in Uganda at the Delivery Unit and Operating Theatre of the Department of Obstetrics and Gynaecology at Mulago National Referral Hospital, Kampala, which has about 25,000 annual deliveries.

Inclusion criteria

Inborn infants fulfilling the following inclusion criteria will be eligible to participate in the trial:

- Inborn baby (i.e., born in the hospital)
- Estimated gestational age of at least 34 weeks
- Estimated birth weight of at least 2000 g
- Need for PPV at birth (based on HBB algorithm)
- Parental consent.

Exclusion criteria

- Major malformations (incompatible with sustained life or affecting the airways)
- Macerated stillbirth.

Primary outcome measures

- A composite outcome of (a) 7-day mortality or (b) admission to neonatal intensive care unit (NICU) with neonatal encephalopathy (maximum Thompson score of 11 or above at day 1–5 during hospitalization) or both [36–38].

Secondary outcome measures

- Safety of i-gel® in the hands of lower cadre (non-doctor) birth attendants: adverse events (AEs) and serious adverse events (SAEs)
- Time to initiate PPV
- Heart rate at 0, 60, 90, 120, 180, 240, and 300 s
- Advanced resuscitation (chest compressions, intubation, and drug delivery), including intervention by supervising physician
- Early neonatal death (<7 days)
- Very early neonatal death (<24 h)
- Neonatal encephalopathy: admission to NICU with a Thompson score of 11 or above during day 1–5 during hospitalization
- Neonatal encephalopathy: admission to NICU with a Thompson score of 7 or above at day 1–5 during hospitalization
- Any hospital admission during the first 7 days of life.

Procedures

Prior to interventions: training midwives

Two hundred members of the staff involved in neonatal resuscitation participated in a modified HBB (2nd edition) one-day course [5] during two weeks in November 2017. The course was held by two pediatricians familiar with the use of supraglottic airway devices and was facilitated by two or three local HBB instructors. It consisted of a review of the HBB action plan and practical hands-on skill stations. The HBB

training includes simulation scenarios involving key procedures of the action plan (thermal loss prevention, stimulation, clinical assessment, airway management, etc.) and the use of the FM (Laerdal silicon resuscitator, Laerdal Medical, Stavanger, Norway). An additional module for training on the use of the i-gel® (Intersurgical Ltd.) was added. A high-fidelity model (SimNewB Laerdal manikin, Laerdal Medical) was used to train the staff in the use of both devices (i-gel® and FM). SimNewB provides realistic airways and good feedback with chest rise when effective PPV is provided. The participants learned the insertion technique recommended by the manufacturer that is the same in the manikin and in the neonate [26, 32]. A silicon lubricant (not needed in newborn infants because of oral secretions) facilitated the procedure. Three successful i-gel® insertions in the manikin were required to partake in the study. FM ventilation was taught in accordance with the HBB curriculum using the NeoNatalie manikin (Laerdal Medical) and included advanced corrective measures. In case of failed FM ventilation, the participants were instructed to apply the following measures before considering the alternative airway device: reapplication of the mask, repositioning of the head, and increase of the inspiratory pressure. The use of suctioning was de-emphasized in accordance with the latest guidelines.

Recruitment and implementation

Investigators and trained research assistants will participate in the enrollment of participants in accordance with the inclusion criteria (Fig. 1). Neonates will be recruited every day around the clock consecutively until sample size is reached. Data from babies will be used in the trial only after written parental consent is given. A senior investigator will be available at all times to discuss concerns raised by parents or clinicians during the course of the trial.

Tagging of newborns

All neonates enrolled in the trial and their mothers will be tagged with a trial bracelet with a unique trial ID number to facilitate matching and retrieval.

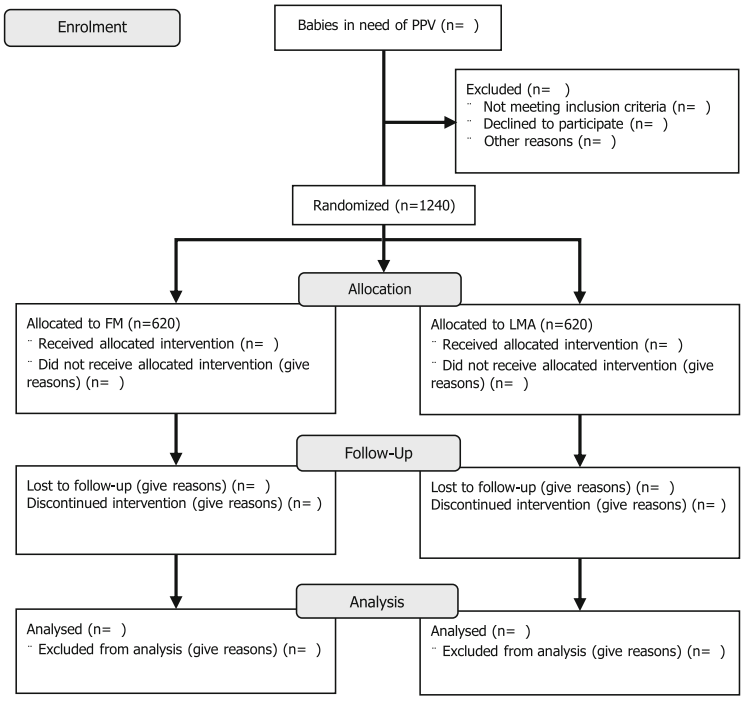

Fig. 1 Trial profile (CONSORT flowchart)

Randomization

Cluster randomization will be used, choosing day-by-day clusters. For practical reasons, individual randomization is not feasible, so all neonates enrolled in the same day (representing a cluster) will be randomly assigned to the same treatment. This approach randomly assigns daily groups of neonates rather than individual neonates, and neonates within any one day are likely to respond in a similar manner; hence, their data cannot be assumed to be independent. The clustering structure of the data was taken into account in sample size calculation and data analysis planning. A randomization list will be made by an independent statistician using block randomization with block sizes of 4–8. The allocation remains concealed until the actual trial day when the randomization envelope is opened by the surveillance officer on duty at 8 a.m. The midwives are informed at the beginning of each shift of the assigned treatment. The envelopes and assignment cards are discarded after use. The assigned procedure will then be performed until the next randomization. To provide proper PPV to the baby, the American Heart Association and European Resuscitation Council guidelines recommend switching to a supraglottic airway device if the resuscitator considers that the FM is failing [17]. We recommend the resuscitator to optimize the ventilation during 3 mins before considering switching ventilation option from FM to i-gel and vice versa, to keep contamination between arms low.

The intervention

Oral consent will be sought for all mothers admitted to the delivery unit, followed by deferred written informed consent as soon as practicable for mothers of babies eligible for the trial. HBB principles of the golden minute will be applied to all babies not crying at birth, including drying, stimulation, and assessment. A stopwatch will be started at the time of birth by a research assistant for all eligible participants. In the case of "baby is not breathing" after initial steps, the midwife will immediately (after cutting the cord) move the babies in need of PPV to the resuscitation area. Inflations will be administered with room air at a rate of 40 to 60/min with a 240-mL silicon self-inflating bag and a pop-off valve limit at 35 cm H_2O (Laerdal Medical). Silicone, round-shaped FM (size 1, Laerdal Medical) or i-gel® (size 1) will be available at each delivery. The duration of resuscitation will be defined as the time period from start of ventilation to the establishment of spontaneous breathing. Heart rate will be registered with a dry-electrode electrocardiogram monitor (NeoBeat Newborn Heart Meter, Laerdal Global Health, Stavanger Norway) featuring fast signal acquisition [39]. All babies with a 5-min APGAR (Appearance, Pulse, Grimace, Activity and Respiration) score of less than 7, respiratory distress, hypothermia (axillary temperature of less than 36.0 °C), or signs of encephalopathy will be transferred to the NICU. Resuscitation data, any contamination between arms, follow-up contact, and admission to the neonatal unit will be recorded by a research assistant. All interventions will be recorded on video to ensure quality assurance and data collection.

Management from supervising physician

Advanced resuscitation can be initiated in accordance with local hospital and International Liaison Committee on Resuscitation (ILCOR) guidelines [34], should a supervising physician be available. This can include use of alternative airways, including ETT, chest compressions, and drug administration.

Contamination between arms

Contamination between arms (switching to the alternative device) will be possible after 3 min of sustained PPV, should ventilation be deemed unsatisfactory. The alternative device will be accessible in an easily accessible box on the resuscitation table. This possible scenario will be practiced during the training. In all cases, a report specifying the reasons for switching to the alternative airway device will be filled out.

Masking

Health-care providers (midwives) performing resuscitation and the research assistant recording resuscitation data in the delivery ward cannot be masked to the allocation arm. However, the examiners assessing neonatal encephalopathy outcomes will be masked to the arm allocation. Outcome examiners will be exclusively working at the NICU, physically separated from where the resuscitations are performed. The arm allocation will not appear on the medical chart. Thus, arm allocation of admitted patients will not be identifiable by the outcome examiner. The independent data monitoring committee (IDMC) will have access to arm allocation when performing interim analysis and assessment of AEs/SAEs. The statistician who will perform data analysis will be masked to treatment allocation.

Sample size

Considering our previous phase II trial, we estimate that a reduction of 25% of adverse outcomes may be possible. A sample size of 954 participants (477 per arm) is required to have a 90% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 40% in the standard-of-care arm to 30% in the supraglottic-airway arm. The sample size is increased to 1150 or 1240 because of the day-by-day cluster randomization, assuming an intra-class correlation of 0.10 and an average daily enrollment of three or four participants, respectively.

Data collection and monitoring

Assessment and collection of outcomes

The primary outcome will be assessed in two parts. Mortality outcome will be collected daily at the NICU for admitted trial patients until day 7. Non-hospitalized participants will receive a scheduled appointment or phone call by a trial nurse with the mother at day 7 assessing the health of the baby. For all hospitalized participants, morbidity by neonatal encephalopathy will be assessed by a trial doctor masked to the arm allocation. This assessment will take place daytime on day 1, 2, 3, 4, and 5 or until discharge, using Thompson score (Table 1).

Data from the pre-coded case report form (CRF) will be entered into Open Data Kit (ODK) (https://opendatakit.org), an open-source suite of tools that helps researchers manage mobile data collection solutions. The data will be stored on an encrypted server and subsequently transferred to a statistical software package for analysis.

The CRFs will be pre-tested before the commencement of the trial. Data from the birth attendants' questionnaire and the CRFs will be filled in by the birth attendants and will be continuously entered into ODK.

Videos will be recorded as a quality control. The neonatal resuscitation algorithm will be put in place to ensure that all interventions are standardized. A proper light source is needed on the table. Headlamps will act as backup in case of a power shortage at night.

Independent data monitoring committee

An IDMC consisting of four members—a statistician, an obstetrician, and two pediatricians—was appointed. They are operating in accordance with the IDMC charter which is developed with the members.

The timing of the interim analysis will be carried out by the IDMC. It will be planned when about half of the events have occurred, following the DAMOCLES (Data Monitoring Committees: Lessons, Ethics, Statistics) group recommendations [40].

The IDMC will ensure that the trial protocol was followed and control the adequacy of enrollment and randomization. The interim data will also assess quality standards and adherence to ethical requirements.

The interim analysis will be performed by the IDMC statistician unmasked to the treatment allocation. Based on this, the IDMC will make recommendations on the continuation of the trial and its modifications or decide on potential termination in case of harm.

Statistical analysis

A detailed statistical analysis plan—based on the principles in this section—will be developed before the statistical analysis of the trial. Data analysis will be performed by using the statistical software packages Stata, SAS, and R. All tests will be two-sided, and a P value of less than 0.05 will be considered statistically significant. Missing data will be considered, and appropriate imputations will be discussed and performed when appropriate. Statistical analysis will include an unadjusted analysis followed by an adjusted analysis. The primary outcome will be compared between the two treatment arms by using the chi-squared test. The secondary outcomes will be compared by using the chi-squared test or Fisher's test (categorical outcomes) and using the Student's t test or Mann–Whitney test (continuous outcomes). Mixed-effect regression models will be estimated to evaluate the effect of the treatment on binary outcomes, adjusting for clusters (random effect) and clinically relevant confounders. Data analyses will be performed on an intention-to-treat (ITT) basis. However,

Table 1 Timeline of the trial

	Enrollment	Allocation	Admission neonatal intensive care unit		Follow-up
Time point	T-1	Day 0	Day 1	Day 2–5	Day 7
Enrollment					
Eligibility screen	×				
Prior oral consent	×				
Deferred consent			×		
Randomization		×			
Interventions					
Resuscitation		×			
Assessments					
Active monitoring of resuscitation		×			
Video recording		×			
Neurological status			×	×	
Mortality assessment			×	×	×

since the trial is prone to some contamination (i.e., the person resuscitating may decide to shift to the other device) which can be limited by appropriate training but not entirely prevented, a per-protocol analysis and a contamination-adjusted ITT analysis will also be performed. These results will be considered along with the primary ITT analysis when drawing the conclusions of the trial. Subgroup analyses—per treatment center, time of the day (i.e., day/night), and per birth mode—will be carried out with exploratory purpose.

Safety

Resuscitations will be continuously monitored by video and observed by the attending midwife or physician and the researcher assistant in order to detect AEs and SAEs. Safety measures will include monitoring of SAEs and detection of unexpected changes in incidence of common neonatal complications. The AEs will be managed by the attending hospital physician/midwife/researcher and followed until resolution or until a stable clinical endpoint is reached by the clinician responsible for the care of the recruited patient.

If there is a reasonable suspected causal relationship with the intervention, SAEs will be reported to the Mulago Research and Ethics Committee (MREC) to guarantee the safety of the participants. Any suspected unexpected serious adverse reactions (SUSARs) with or without a reasonably plausible causal relationship with use of the supraglottic airway will also be reported to the MREC.

Ethical considerations

The protocol was approved by the institutional review board of Mulago National Referral Hospital, Uganda; the Uganda National Council of Science and Technology; the Director General from the Ministry of Health, Uganda (MREC 1168); and the Regional Committee for Medical and Health Research Ethics (REK South East reference number 2017/989) in Norway.

Extensive discussions with clinical experts and members of the ethical board were necessary to solve the problem of obtaining consent without delaying the intervention. A two-tier procedure for consent will be implement in this trial because it involves unexpected care of critically ill newborns. All mothers entering the labor ward irrespective of whether their baby is suspected of filling inclusion criteria will receive brief information of the trial after which oral consent will be sought. Mothers whose infants are found eligible at birth will be approached for full written deferred consent for continuing participation. All information, including informed consent and the material used in the trial, will be translated in English and Luganda in a clearly understandable form. A senior investigator will be available to discuss any additional questions regarding the trial.

Sustainability and scalability

A simplified neonatal resuscitation program that can reduce neonatal deaths due to perinatal asphyxia is the highest newborn global health research priority beyond 2015 [41]. This trial will try to demonstrate the first phase of scalability of an innovative approach to newborn resuscitation.

The training module for supraglottic airway use can easily be integrated to current neonatal resuscitation programs [33]. The cost-effectiveness of a supraglottic airway in a low-resource setting needs to be assessed. Such an investment can be justified only if there is a substantial difference between the supraglottic airway and FM. We estimate that a 25% reduction in adverse outcomes is a clinically significant difference large enough to have policy implications. A reusable cuffless device is already available but is still cost-prohibitive [29], so it will be crucial to explore how the unit cost can be reduced. A historical parallel could be the substantial drop in the cost of antiretroviral therapy against HIV over the last decades [42], allowing scale-up of treatment to a level that previously seemed impossible in low-resource settings.

Discussion

Newborn resuscitation training and simulation-based curriculum show mixed results in relation to their impact on newborn mortality [3, 4] and their effect on neurological morbidity remains unknown [43]. Further improvement of neonatal resuscitation performance is crucial.

This large trial is the first to assess the impact on mortality/morbidity of the use of a supraglottic airway device during neonatal resuscitation. It is powered to 90% and designed to add evidence lacking in this field. To the best of our knowledge, only four RCTs comparing LMA or supraglottic airway to FM ventilation including 636 patients have previously been published [18, 19, 25, 26, 32]. They have focused mainly on vital sign outcomes or successful resuscitation [34]. Safety and long-term outcomes remain important knowledge gaps. This task-shifting intervention involves midwives as they are the frontline health workers in many settings where newborn mortality is high. The burden of disease from intrapartum-related events can be reduced if simple and robust technologies for newborn resuscitation can be identified [44].

The trial will also monitor neonatal outcome data until day 7. We hypothesize that effective ventilation will be easier to perform with the supraglottic airway device and significantly decrease early neonatal mortality and brain damage from neonatal encephalopathy. Results from this large trial will contribute to provide evidence that can help define best practice advice for future guidelines.

Trial status

The trial started recruiting participants on May 8, 2018.

Additional file

Additional file 1: SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. (DOCX 63 kb)

Abbreviations

AE: Adverse event; CRF: Case report form; ETT: Endotracheal tube; FM: Face mask; HBB: Helping Babies Breathe; IDMC: Independent data monitoring committee; ITT: Intention-to-treat; LMA: Laryngeal mask airway; MREC: Mulago Research and Ethics Committee; NICU: Neonatal intensive care unit; ODK: Open data kit; PPV: Positive pressure ventilation; RCT: Randomized controlled trial; SAE: Serious adverse event

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Authors' contributions

TT, NJP, SMH, JB, JN, CL, DT, GS, TA, HE, and MB initiated the trial design and helped with implementation. TT is grant holder. FC provided statistical expertise in clinical trial design and will conduct the primary statistical analysis. All authors contributed to refinement of the trial protocol and read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Competing interests

The authors have no financial relationship relevant to this article to disclose. TT, NP, SMH and TA are co-founders of the non-profit organization tap4life.org, which produces the free application NeoTapLS, www.tap4life.org.

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