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Title:
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Date:
2020-10-05

Citation:
Hodgson, K. A., Owen, L. S., Kamlin, C. O., Roberts, C. T., Donath, S. M., Davis, P. G. & Manley, B. J. (2020). A multicentre, randomised trial of stabilisation with nasal high flow during neonatal endotracheal intubation (the SHINE trial): A study protocol. BMJ Open, 10 (10), https://doi.org/10.1136/bmjopen-2020-039230.

Persistent Link:
https://hdl.handle.net/11343/252202

BMJ Open

A multicentre, randomised trial of stabilisation with nasal high flow during neonatal endotracheal intubation (the SHINE trial): a study protocol

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To cite: Hodgson KA, Owen LS, Kamlin CO, *et al*. A multicentre, randomised trial of stabilisation with nasal high flow during neonatal endotracheal intubation (the SHINE trial): a study protocol. *BMJ Open* 2020;**10**:e039230. doi:10.1136/bmjopen-2020-039230

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-039230).

Received 08 April 2020
Revised 31 July 2020
Accepted 11 September 2020

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ABSTRACT

Introduction Neonatal endotracheal intubation is an essential but potentially destabilising procedure. With an increased focus on avoiding mechanical ventilation, particularly in preterm infants, there are fewer opportunities for clinicians to gain proficiency in this important emergency skill. Rates of successful intubation at the first attempt are relatively low, and adverse event rates are high, when compared with intubations in paediatric and adult populations. Interventions to improve operator success and patient stability during neonatal endotracheal intubations are needed. Using nasal high flow therapy extends the safe apnoea time of adults undergoing upper airway surgery and during endotracheal intubation. This technique is untested in neonates.

Methods and analysis The Stabilisation with nasal High flow during Intubation of NEonates (SHINE) trial is a multicentre, randomised controlled trial comparing the use of nasal high flow during neonatal intubation with standard care (no nasal high flow). Intubations are randomised individually, and stratified by site, use of premedications, and postmenstrual age (<28 weeks' gestation; ≥28 weeks' gestation). The primary outcome is the incidence of successful intubation on the first attempt without physiological instability of the infant. Physiological instability is defined as an absolute decrease in peripheral oxygen saturation >20% from preintubation baseline and/or bradycardia (<100 beats per minute).

Ethics and dissemination The SHINE trial received ethical approval from the Human Research Ethics Committees of The Royal Women's Hospital, Melbourne, Australia and Monash Health, Melbourne, Australia. The trial is currently recruiting in these two sites. The findings of this study will be disseminated via peer-reviewed journals and presented at national and international conferences.

Trial registration number ACTRN12618001498280.

Strengths and limitations of this study

- The first randomised controlled trial of nasal high flow to improve procedure success and physiological stability during neonatal intubation.
- A low risk, easily generalisable intervention to assist with a difficult, life saving procedure.
- Interventions are video recorded to enable accurate and objective data collection.
- Likelihood of intubation success may be affected by operator experience and the use of videolaryngoscopy; these factors will be addressed in a sensitivity analysis.
- Due to the nature of the intervention, blinding is not possible.

INTRODUCTION

Opportunities for clinicians to acquire proficiency in neonatal endotracheal intubation have decreased over time.[1 2] The increased use of 'non-invasive' respiratory support (without an endotracheal tube), less-invasive surfactant administration techniques, and the move away from routine endotracheal suctioning of babies born through meconium-stained amniotic fluid have contributed to this trend. In extremely preterm infants, the use of nasal continuous positive airway pressure (CPAP) for primary respiratory support results in fewer days of mechanical ventilation, less surfactant administration and a lower risk of bronchopulmonary dysplasia, compared with intubation and mechanical ventilation.[3 4] Nasal high flow therapy (nHF) is a newer mode of non-invasive respiratory support that delivers heated, humidified gas via two small nasal prongs. In preterm infants, nHF has been evaluated for the management of early respiratory distress and post extubation support, leading to widespread use in neonatal intensive care units (NICUs).[5 6] Nasal HF is commonly used in preterm and term newborn infants,[5 6] as well as in children[7] and adults.[8] Current clinical applications of nHF in neonates include primary support of respiratory distress syndrome and post-extubation support in preterm infants.[9]

While non-invasive modes of respiratory support are used whenever possible for neonates, endotracheal intubation is still sometimes required, particularly for the most immature infants.[10] With decreasing clinical experience in this procedure, neonatal intubation success rates at the first attempt are low but increase with increasing operator experience. In a large international registry study of adverse events (AEs) associated with endotracheal intubation, Foglia *et al* demonstrated that overall first attempt intubation success was 49% for intubations in the NICU.[11] O'Donnell *et al* reviewed 60 intubation attempts and reported success rates of 24% for residents (junior trainees), 78% for fellows (senior trainees) and 86% for consultants.[12] Furthermore, the duration of neonatal intubation attempts is often longer than the international guidelines recommend[13] and varies with the experience of the operator.[12] Neonates are often clinically unstable during endotracheal intubation, due to a lower functional residual capacity and greater metabolic demand than older children and adults.[14] In one study, severe hypoxaemia (defined as peripheral oxygen saturation (SpO_2)<60%) was reported in 44% of neonatal intubations, and bradycardia (heart rate <60 bpm for at least 5 s) in 24%.[15]

Apnoeic oxygenation refers to oxygenation in the absence of spontaneous respiration or positive pressure ventilation.[16] The physiological principle underlying apnoeic oxygenation is aventilatory mass flow: in the apnoeic patient, as oxygen moves from the alveoli into the bloodstream, alveolar pressure becomes subatmospheric.[17] This in turn facilitates movement of oxygen (applied via nasal prongs) down a pressure gradient from the atmosphere into the alveoli. Apnoeic oxygenation is used as an adjunct to preoxygenation in anaesthesia, to prolong the period of time prior to desaturation in patients in whom definitive securing of the airway is expected to be difficult (due to anatomy),[17] impossible (due to airway surgery),[18] or the time to desaturation short (due to patient comorbidities).[17]

Traditionally apnoeic oxygenation was provided via 'low flow' nasal cannulae. More recently, the concept of Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) has arisen. THRIVE is the use of nHF (heated, humidified air and oxygen via nasal cannulae) during apnoea. There is evidence that nHF use during apnoea may improve oxygenation and also carbon dioxide clearance, compared with 'low flow' oxygen or jaw support only.[17 18] Proposed mechanisms include removal of carbon dioxide through enhanced dead space washout and continuous distending pressure, which increases the pressure gradient for oxygen to move down. Furthermore, apnoeic ventilation may be facilitated by cardiogenic oscillations, whereby variations of heart volume during the cardiac cycle promote gas exchange by altering intrathoracic pressure.[19 20] Turbulent gas flow from nHF, combined with compression and expansion of the alveoli due to blood flow in the pulmonary vasculature, may allow some gas exchange during apnoea.[19]

THRIVE has been shown to prolong the safe apnoeic time (time prior to desaturation) in adults[17] and in healthy infants and children undergoing general anaesthesia and elective intubation.[21] Two randomised controlled trials have examined THRIVE in the paediatric population. Humphreys *et al* randomised 48 children aged <10 years undergoing general anaesthesia to THRIVE (nHF at 2 L/kg/min for patients up to 15 kg), or to control (jaw support only). THRIVE significantly prolonged the apnoea time (time prior to SpO_2 <92%) in all age groups.[21] All but one patient in the control group desaturated to <92% within the anticipated time frame, which was predefined as twice the length of previously published age-related values.[22] In contrast, the THRIVE group had no desaturations and a mean SpO_2 of 99.6% (range 97%–100%). Riva *et al* randomised 60 patients aged 1–6 years undergoing general anaesthesia to receive one of three methods of apnoeic oxygenation: low flow oxygen (0.2 L/kg/min FiO_2 1.0), THRIVE 100% (nHF at 2 L/kg/min FiO_2 1.0) or THRIVE 30% (nHF at 2 L/kg/min FiO_2 0.3). The primary outcome was apnoea time (time prior to SpO_2 <95%). Additional reasons for termination of the intervention were apnoea time of 10 min or hypercarbia (partial pressure of carbon dioxide >65 mm Hg). Apnoea time was longer in low flow and THRIVE 100% groups, compared with the THRIVE 30% group. While there was no statistically significant difference between the THRIVE 100% and the low flow groups, the reason for termination of apnoea was time or hypercarbia in all THRIVE 100% oxygen patients, not the primary outcome of desaturation.

There are currently no published studies of the use of THRIVE during neonatal intubation, nor in emergency settings in older patients with respiratory distress. The aim of the Stabilisation with nasal High flow during Intubation of NEonates (SHINE) randomised controlled trial is to investigate whether the use of nHF during neonatal endotracheal intubation (1) after birth in the delivery room and (2) in the NICU improves the likelihood of successful intubation on the first attempt without physiological instability of the infant.

METHODS AND ANALYSIS

Study design

A multicentre, unblinded, randomised controlled trial investigating the efficacy of nHF to improve success and stability during neonatal endotracheal intubation. Intubations performed in the delivery room or NICU will be randomised, with a 1:1 ratio. Infants will either receive nHF during the endotracheal intubation attempt, or standard care (no nHF). Intervention will be applied for the first intubation attempt of the episode only.

Sample size

The sample size of 246 infants is based on a study of videolaryngoscope use for teaching neonatal intubation,[23] which examined 206 intubations by junior medical staff.

This study reported a 29% successful intubation rate at the first attempt without desaturation >20% or bradycardia <100 bpm. With a power of 90% to detect an increase in the incidence of successful intubation without physiological instability from 30% to 50%, 123 infants in each group (246 total) are required.

There is some variability in the reporting of success rates for neonatal intubation, depending on level of operator experience[12] and use of videolaryngoscopy.[23] The uncertainty surrounding the baseline rate of the primary outcome may present a limitation in this study.

Patient population

Any neonate undergoing endotracheal intubation in the delivery room or NICU is eligible for inclusion. In participating centres, all infants who undergo endotracheal intubation will be screened for study eligibility. Infants already studied can have subsequent intubation episodes randomised again if (1) the premedication randomisation stratum differs between intubations, or (2) there is at least 1 week between the studied intubations for intubations using premedications.

Inclusion criteria

Infants undergoing endotracheal intubation in the delivery room or NICU are eligible for inclusion.

Exclusion criteria

Exclusion criteria are:

- Planned nasal intubation.
- A requirement for immediate endotracheal intubation as determined by the treating clinician (insufficient time for researcher to randomise and set up study equipment).
- Heart rate <120 bpm prior to randomisation (as at higher risk of bradycardia as defined in the trial).
- Contraindications to nHF use, for example, congenital nasal anomaly, congenital diaphragmatic hernia or abdominal wall defect.
- Cyanotic congenital heart disease.
- Infant with suspected or proven COVID-19, or born to a mother with suspected or proven COVID-19.

Randomisation

Each intubation episode is randomised to one of the two groups using random permuted blocks with varying block sizes. Prerandomisation stratification is by centre, postmenstrual age (<28 weeks; ≥28 weeks) and use of premedication for intubation. To enable rapid randomisation following the decision to intubate by the clinical team, the randomisation is performed at the cotside using a smartphone or computer with online access to the REDCap[24] randomisation tool.

CLINICAL MANAGEMENT

Nasal HF group (intervention)

A trial investigator will perform the intervention. Immediately prior to intubation, infants will be receiving either CPAP via nasal prongs, nasal mask or a face mask, or positive pressure ventilation via a face mask. The Precision Flow device (Exeter, New Hampshire) and weight-appropriate binasal cannulae will be used to provide nHF. The cannulae will occupy approximately 50% of the nares and enable leak. The investigator will apply the nHF prongs at the time of the face mask, nasal mask or nasal prongs being removed for laryngoscopy. Gas flow will be set to 8 L/min for the duration of the study intervention. The fraction of inspired oxygen (FiO_2) prior to the intubation attempt, including the use of any preoxygenation (an increase in FiO_2 prior to the intubation attempt), will be at the discretion of the clinical team. The trial investigator will set the nHF FiO_2 to the same amount the infant was receiving prior to laryngoscopy, and if the infant desaturates to <90% during the intubation attempt, the investigator will increase the nHF FiO_2 to 1.0 (100% supplemental oxygen) until the end of the intubation attempt. The nHF prongs will be secured only by tightening the cannula tubing behind the infant's head; no adhesive tapes will be applied to the face. Nasal HF will continue during laryngoscopy, and the investigator will remove the nHF prongs when the first intubation attempt is either ceased, or successfully completed (see definition below). The commencement, duration and termination of an intubation attempt will be at the discretion of the most senior clinician caring for the infant.

Standard care group (control)

Patients in the control arm will receive standard care. The intubation attempt (laryngoscopy) will proceed without the application of nHF or the use of supplemental oxygen. In the event that an infant in the NICU is already receiving respiratory support from nHF prior to intubation being planned, this may continue up until the time of induction medications being administered (if applicable). The commencement, duration and termination of an intubation attempt will be at the discretion of the most senior clinician caring for the infant.

OUTCOMES

Primary outcome

The primary outcome is the incidence of successful intubation at the first attempt without physiological instability.

Definitions:

- Intubation attempt: the insertion of the laryngoscope blade beyond the infant's lips.
- Intubation duration: the time from the insertion of the laryngoscope blade beyond the infant's lips until the removal of the laryngoscope blade from the infant's mouth.
- Successful intubation: the completion of the intubation attempt with correct positioning of the endotracheal tube confirmed by detection of expired carbon dioxide on a colorimetric detector.
- Physiological instability: the incidence (any duration) of an absolute decrease in SpO_2 >20% from baseline

(immediately prior to the intubation attempt), and/or bradycardia (heart rate <100 bpm), during the first intubation attempt.

Secondary outcomes

1. Incidence of successful intubation on the first intubation attempt.
2. Incidence of desaturation (absolute decrease in SpO_2 >20% from baseline) *or* bradycardia (heart rate <100 bpm) during the first intubation attempt.
3. Time to desaturation (absolute decrease in SpO_2 >20% from baseline) during the first intubation attempt in seconds.
4. Time to bradycardia (heart rate <100 bpm) during the first intubation attempt in seconds.
5. Duration of desaturation (absolute decrease in SpO_2 >20% from baseline) during first intubation attempt in seconds.
6. Duration of bradycardia (heart rate <100 bpm) during first intubation attempt in seconds.
7. Median SpO_2 during intubation attempt.
8. Median heart rate during intubation attempt.
9. Duration of SpO_2 >97% during intubation attempt, in seconds.
10. Number of intubation attempts.
11. Duration of all intubation attempts (successful and unsuccessful), in seconds.
12. Incidence of cardiac compressions and/or epinephrine administration within 1 hour after the first intubation attempt.
13. Incidence of pneumothorax within 72 hours after randomisation, diagnosed either by transillumination of the chest and/or by chest X-ray.
14. Incidence of pneumothorax requiring drainage (via needle thoracocentesis or insertion of an intercostal catheter) within 72 hours after randomisation.
15. Death within 72 hours after randomisation.

Data analysis plan

The incidence of the primary outcome will be compared using risk difference and two-sided 95% CI. Secondary outcomes will be compared using risk difference (with 95% CI) (outcomes 1, 2 and 9–12), and difference of means or medians with 95% CI (outcomes 3–8). Planned subgroup analyses by each of the prerandomisation strata will be performed for the primary outcome and selected secondary outcomes. Analyses will be by intention-to-treat, with an additional per-protocol analysis for the primary outcome. The primary analysis will be adjusted for stratification factors. Regression models with the stratification factors used in randomisation included as covariates will be used for all analyses. A sensitivity analysis will be conducted to account for repeated randomisation events within individual subjects. If an imbalance in demographics known to affect intubation success (eg, postmenstrual age, weight, videolaryngoscope use, operator experience) is detected, a further sensitivity analysis adjusting for the relevant demographics will be conducted. Data will be exported from an electronic database to an electronic statistical package for analysis.

Ethics and dissemination

Prospective consent will be sought from a parent for inclusion of their infant in the study, whenever possible. Prospective consent will be obtained for all eligible intubation episodes through the course of the infant's stay in NICU, in the event that multiple intubations are required for the same patient. In the event of emergent intubation in the delivery room or within the first 24 hours after admission to NICU, it may not be practical to obtain prospective informed consent. In these situations, the study has approval to use a retrospective consent process at both study sites. The infant will be included in the study, then consent to continue (retrospective consent) will be sought from a parent or guardian as soon as possible after the procedure. This consent process was pursued due to the known safety and efficacy of nHF use in neonates, and the lack of any anticipated risk compared with standard clinical practice. Furthermore, obtaining prospective written consent from parents or guardians of infants undergoing intubation in the delivery room or the NICU is not always practical, as they may require intubation quickly and unpredictably. The SHINE trial received ethical approval from the Human Research Ethics Committees of The Royal Women's Hospital, Melbourne, Australia and Monash Health, Melbourne, Australia.

Video recording

The intubation will be video recorded in order to optimise the quality of data collection. A GoPro (GoPro, San Mateo, California) video camera will be placed in a location that provides a clear overhead view of the intubation procedure, the infant's face and the Masimo pulse oximeter displaying real time SpO_2 and heart rate data, with averaging time of 2 s and set at maximum sensitivity. The study investigator will record data on a Case Report Form (CRF) and verify this against the video recording. Corrections will be made where errors are identified. The study investigator will also record the observed primary outcome in real time by, in case of video failure. An independent assessor will also review the video footage to verify the primary outcome. Any discrepancies or disagreements will be resolved by a third assessor from the trial steering committee. Additional consent will be obtained from the parent or guardian to use the video for the purposes of the study and for educational or research purposes. Consent will also be obtained from the staff member performing the intubation for the video to be used.

Patient and public involvement

The study was discussed with parents of infants who had undergone endotracheal intubation in the neonatal unit during a pilot phase, prior to commencement of the trial, in order to assist with study design and to determine the acceptability of the intervention and trial procedures.

Adverse events

AEs will be captured from the time of randomisation until the time the infant is successfully intubated. AEs are recorded as part of the study design, and AEs are components of the primary and secondary outcomes of the study. The investigator will be responsible for recording all AEs, regardless of their relationship to the intervention. Conditions that are present at screening and do not deteriorate will not be considered AEs.

The following AEs will be collected and recorded on the CRF:

1. Desaturation: absolute decrease in oxygen saturation >20% from baseline.
2. Bradycardia: heart rate falling below 100 bpm.
3. Oesophageal intubation: misplacement of endotracheal tube.
4. Difficult intubation: defined as intubation requiring two or more intubation attempts

Serious AEs

Serious AE (SAEs) will be captured from the time of randomisation until 72 hours after randomisation. All SAEs will be reported to the ethics committee within 24 hours of occurring.

SAEs are defined as:

1. Death within 72 hours after the randomised intubation attempt.
2. Cardiopulmonary resuscitation and/or epinephrine administration within 1 hour of the randomised intubation attempt.
3. Newly diagnosed pneumothorax requiring drainage within 72 hours of the randomised intubation attempt.

Study oversight

A data safety monitoring board (DSMB) was established prior to the commencement of the trial and consists of two independent neonatologists and an independent statistician. The DSMB will review the safety of the trial at interim analyses after the primary outcome is known for 60, 125 and 180 patients (~25%,~50% and~75% recruitment). An additional efficacy analysis of the primary outcome only will be conducted after the primary outcome is known for 125 patients (~50% recruitment). The DSMB may recommend ceasing the trial if there is a highly statistically significant difference ($p<0.001$) in the incidence of the primary outcome between the groups, or an important difference in the incidence of AEs or SAEs. The DSMB will also consider any new evidence that may make continuing the trial unethical.

Clinical significance

Endotracheal intubation is a life-sustaining intervention. However, acquiring this skill is becoming increasingly difficult as the learning opportunities for an individual trainee decline. Many attempts are curtailed because of patient instability leading to loss of confidence among neonatal trainees. Improving the success rates of neonatal endotracheal intubation and maintaining cardiorespiratory stability during the attempt is important to minimise morbidity for all, but especially for preterm newborn infants. If effective and safe, nHF use during neonatal intubation can be rapidly translated into clinical practice as it is simple to use and readily generalisable to units with access to this equipment. Results from this study will be disseminated via peer-reviewed journals and presented at national and international scientific conferences.

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Contributors KAH conceptualised and designed the trial protocol, and drafted and revised the manuscript. LSO, COK, CTR, PGD and BJM contributed to study design and revised the protocol manuscript. SMD designed the statistical analysis and revised the manuscript. All authors have read and approved the final manuscript and are accountable for its accuracy.

Funding This work was supported by National Health and Medical Research Council program grant #1113902. Nasal high flow equipment and consumables have been supplied by Vapotherm.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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