SURFactant Administration by SUPraglottic Airway (the SURFSUP Trial): SURFSUP 1 Protocol

Coordinating Principal Investigator (CPI)

Dr Calum Roberts, Monash Health

Chief Investigators (CIs)

A/Prof Adam Buckmaster, Gosford Hospital
A/Prof Kim Dalziel, University of Melbourne
Prof Peter Dargaville, Royal Hobart Hospital
Dr Miranda Davies-Tuck, Hudson Institute of Medical Research
Prof Peter Davis, The Royal Women's Hospital
A/Prof Brett Manley, The Royal Women's Hospital
Dr Joyce O'Shea, The Royal Hospital for Sick Children, Glasgow
A/Prof Louise Owen, The Royal Women's Hospital
Prof Charles Christoph Roehr, Southmead Hospital, Bristol

Associate Investigators (AIs)

Dr Manish Agarwal, Ballarat Health Services
Dr Catherine Allgood, Campbelltown Hospital
Dr Risha Bhatia, Monash Health
Dr Douglas Blank, Monash Health
A/Prof Wei Qi Fan, Northern Hospital
Dr Alice Fang, Eastern Health
Mrs Amie Goodwin, Consumer Representative, Monash Newborn
Dr Li Huang, University of Melbourne
Dr Luke Jardine, Mater Mothers
Dr Ansar Kunjunju, Wollongong Hospital
Dr Isaac Marshall, University Hospital Geelong
Dr Helen McDevitt, The Royal Hospital for Sick Children, Glasgow
Dr Mahmoud Montasser, Wishaw General Hospital, Glasgow
Dr Itamar Nitzan, Shaare Zedek Medical Center, Jerusalem
Dr David Quine, Royal Infirmary of Edinburgh, Edinburgh

Site Investigators (SIs)

Those individuals who contribute significantly to the conduct of the trial as site investigators will be named as 'SURFSUP Investigators' at publication of the results manuscript.

Data Safety Monitoring Committee (DSMC)

Prof Frank Bloomfield, Neonatologist, The University of Auckland, Auckland (Chair)
Dr Leah Hickey, Neonatologist, The Royal Children's Hospital, Melbourne
Dr Anneke Grobler, Murdoch Children's Research Institute, Melbourne

Registration

WHO Universal Trial Number: U1111-1258-2109
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1 Trial Summary

1.1 Brief Trial Synopsis

Aim	To evaluate the effectiveness and safety of surfactant administration via supraglottic airway, compared with standard surfactant administration methods via laryngoscopy, in preterm infants with respiratory distress syndrome
Design	Unblinded, multi-centre, randomised controlled trial.
Research Questions	**Primary:** Is surfactant administration via supraglottic airway non-inferior to minimally invasive surfactant therapy (MIST) in preventing need for mechanical ventilation or repeat surfactant within 72 hours, in preterm infants with respiratory distress syndrome? **Secondary:** Compared with MIST, can surfactant administration via supraglottic airway be performed: • With a low rate of physiological instability • Without an increase in adverse events • With a high rate of procedural success
Population	Preterm infants aged <48 hours, with birth weight ≥1250 g, with a diagnosis of RDS, receiving FiO_2 ≥0.30 on non-invasive respiratory support
Setting	Neonatal units capable of providing MIST as standard care. Initial recruitment will be at Monash Children's Hospital (MCH) and the Royal Women's Hospital (RWH), Melbourne
Intervention	First surfactant administered via supraglottic airway
Control	First surfactant administered via laryngoscopy, using minimally invasive surfactant therapy (MIST).
Outcomes	**Primary Outcome** Rate of mechanical ventilation or repeat surfactant within 72 hours of randomisation

	Secondary Outcomes (selected) - Procedural outcomes including desaturation, bradycardia, number of attempts, clinician satisfaction, infant comfort, use of chest compressions - Total surfactant dose - Reason for intubation and mechanical ventilation (if applicable) - Duration of respiratory support - Duration of supplemental oxygen - Pneumothorax requiring drainage - Death during hospital admission - Duration of hospital admission
Sample Size	With an expected rate of mechanical ventilation or repeat surfactant treatment of 24% in both the control group and the supraglottic airway group, then 474 infants per group will be required, with 90% power and a two-sided 95% confidence interval, to demonstrate non-inferiority with a margin of 9%. A total sample of 1000 infants will be recruited to account for a small number of exclusions from the per-protocol analysis

1.2 Plain Language Summary

Respiratory distress syndrome (RDS) is a condition found commonly in babies born prematurely, which results in breathing difficulty soon after birth, due to immaturity of the lungs. Many babies will be managed successfully with breathing support alone, but some require additional treatment with surfactant. Surfactant is a liquid medicine that is given directly into the baby's airway (wind pipe), which helps open the lungs to make breathing easier

Currently, the standard way to give surfactant requires laryngoscopy. This is where a doctor looks directly into the baby's airway using a laryngoscope (a metal device that holds the airway open) and then inserts a tube (catheter) through the vocal cords into the airway to deliver the surfactant treatment. This method is very effective, but is challenging to learn, and may take more than one attempt even for experienced doctors. Also, during laryngoscopy, some babies may briefly have a drop in their heart rate or oxygen levels.

'Supraglottic airways' are a different type of device, made from a soft plastic, shaped to fit into the mouth and form a seal over the airway opening, without passing through the vocal cords. They can be inserted without using a metal laryngoscope, they may be easier for doctors to use and more comfortable for babies. Previous research suggests that surfactant treatment can be given through a supraglottic airway, but we do not yet know if this method is as effective as using standard laryngoscopy.

This research study will compare the new method, supraglottic airway surfactant treatment, with the current standard method, laryngoscopy. We will measure how stable babies are during surfactant treatment, including their oxygen levels and heart rate. We will also record how many babies need additional breathing support (ventilation by a breathing tube) after their surfactant treatment, to determine how effective the treatment is in helping babies with respiratory distress. If supraglottic airway surfactant treatment can be used safely and effectively, and is more comfortable and easier to use, it could become the preferred method of surfactant treatment for babies.

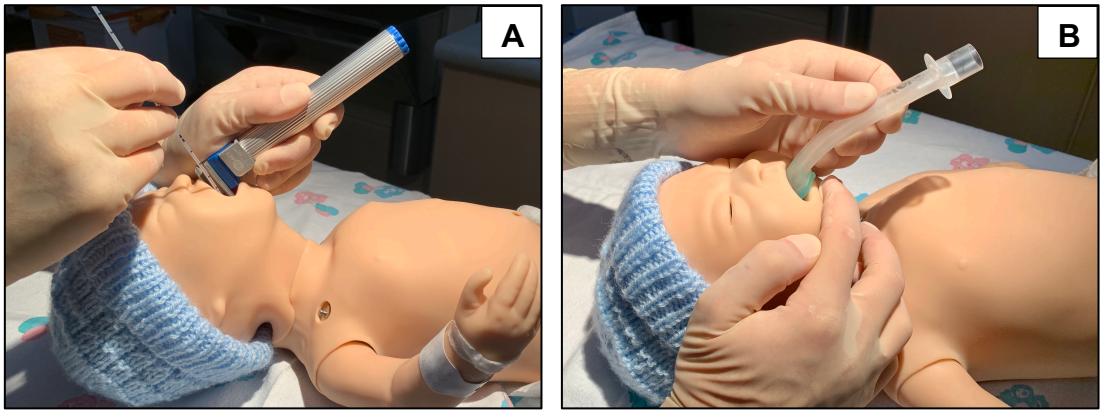

Figure 1. Demonstration of treatment methods on a training manikin
A. Current method using laryngoscope and surfactant catheter B. New method using supraglottic airway

2 Background

2.1 Treatment of Respiratory Distress Syndrome

Current international recommendations for the treatment of preterm infants with respiratory distress syndrome (RDS) suggest avoiding endotracheal mechanical ventilation (MV), instead emphasising the use of non-invasive respiratory support.(1, 2) Approaches favouring the use of non-invasive modalities, such as nasal continuous positive airway pressure (CPAP) or nasal High Flow (nHF), rather than elective intubation, may result in reduced rates of adverse outcomes including bronchopulmonary dysplasia (BPD).(3)

However, non-invasive modes will not provide sufficient support for many infants and they will require intubation and MV. Amongst very preterm infants (born <32 weeks' gestation) treated with early CPAP in Australia and New Zealand, those intubated within 72 hours of birth had increased rates of death or major disability (defined as BPD, grade III-IV intraventricular haemorrhage, cystic brain injury, or retinopathy stage 2 or higher) than those who were successfully managed on CPAP.(4) RDS also remains an important contributor to morbidity and mortality in more mature infants, predisposing to complications such as pneumothorax, and in some cases necessitating prolonged hospital stay or inter-hospital transfer.(5, 6) Risks are particularly high in low- and middle-income settings, where mortality can exceed 50%.(7)

Exogenous surfactant is an effective treatment for RDS, traditionally administered via an endotracheal tube. Clinicians have evaluated several approaches with the aim of combining the benefit of surfactant treatment with that of early CPAP, maximising the chance of avoiding MV and therefore of avoiding adverse outcomes. These include intubation followed by early extubation (commonly referred to as intubation-surfactant-extubation, or INSURE),(8) or the use of a thin catheter to administer surfactant during ongoing nasal CPAP support (known as less invasive surfactant administration, LISA, or minimally invasive surfactant therapy, MIST).(9, 10) Based on increasing evidence from clinical trials,(11) the most recent version of the European RDS guidelines recommends MIST as "the preferred mode of surfactant administration for spontaneously breathing babies on CPAP, provided that clinicians are experienced with this technique".(2) While this guidance is written to apply to infants with RDS across all gestational ages, it is worth noting that the vast majority of infants included in clinical trials of MIST were very preterm, and there are few data available relating to moderate-late preterm infants born 32 weeks' gestation or later.(11)

MIST and INSURE both require skill in laryngoscopy, and are therefore likely to be effective only when performed by operators with substantial experience in performing this technique (typically from previous endotracheal intubations). Whilst this skill is required and relatively commonly performed by senior staff working in tertiary neonatal intensive care units (NICUs), opportunities to establish and maintain competence are much less frequent for clinicians in non-tertiary special care nurseries (SCNs), and for junior trainees even when working in tertiary NICUs. Increasing emphasis on non-invasive support has reduced opportunities for neonatal and paediatric trainees to learn this skill to such a degree, that experts in the field have questioned whether it remains realistic to

expect all non-neonatologist paediatricians caring for newborn infants to be proficient in intubation.(12)
Adverse events are commonly reported during neonatal intubation. In a single-centre NICU report, one or more adverse events were reported in 22% of intubation encounters.(13) It is likely that laryngoscopy without pre-medication is more challenging in infants of greater gestational age and birth weight. However, many such infants will still require surfactant treatment, in both NICUs and SCNs.
Identifying an approach to surfactant administration that is best suited to infants born moderately or late preterm presents an important challenge. Supraglottic airways incorporate an airway tube attached to a small mask that forms a seal around the larynx, and are inserted without the need for laryngoscopy.(14) Studies of supraglottic airway use during resuscitation have shown that they can be successfully inserted by a wide range of providers, including anaesthetists, nurses and paediatricians, with first attempt success rates of 95%.(15-17) Adverse events associated with the use of supraglottic airways have been rare, with several studies reporting that none occurred.(18-22) Supraglottic airways may represent an alternative route for surfactant administration that is easier than direct laryngoscopy, generalisable to a wider group of clinicians, and associated with fewer adverse events. **Provided supraglottic airway surfactant administration is not less effective than methods involving laryngoscopy, it would likely become the preferred technique; this provides the rationale for a non-inferiority trial.**(23)

2.2 Administration of Surfactant via Supraglottic Airway Device

2.2.1 Supraglottic Airway Surfactant vs. Continued CPAP

The most recent Cochrane Review of surfactant administration via supraglottic airway, published in 2011 and not since updated, identified only one small RCT for inclusion.(24) This study in 26 infants was unpublished at the time of the Cochrane Review, but was subsequently published in 2013. Infants of >1200 g at birth, receiving CPAP with fraction of inspired oxygen (FiO_2) 0.30-0.60, were randomised to either supraglottic airway surfactant or continued CPAP treatment, with the primary outcome of intubation. The trial was ceased early due to slow recruitment; at which time the intubation rates did not differ significantly between intervention and control groups (8% vs. 23%, P=0.59). Since 2011 several further RCTs have been published (Table 2). The largest of these similarly compared surfactant administration via supraglottic airway versus continued CPAP treatment, in a group of preterm infants ≥1250 g receiving CPAP for RDS with required FiO_2 0.30-0.40.(19) This study was also ceased early, after recruitment of 103 of the planned 144 infants. Intubation and MV in the first seven days were significantly reduced in the supraglottic airway surfactant group (38% vs. 64%, P<0.01). No adverse events were recorded in either group.

2.2.2 Supraglottic Airway Surfactant vs. Surfactant by Laryngoscopy

Four RCTs, including 228 infants, have compared surfactant administration via supraglottic airway versus administration via endotracheal tube, either by INSURE method or with continuing MV. In three of these studies infants were randomised to receive surfactant by supraglottic airway, or by INSURE.

Sadeghnia(18) et al studied 70 infants of ≥2 kg at birth, receiving CPAP with FiO_2 ≥0.30 for respiratory distress. None of the infants in either group required MV, and other clinical outcomes were similar between groups. Pinheiro(20) et al included 60 preterm infants ≥29 weeks' gestation with RDS, reporting a lower rate of intubation in the supraglottic airway group (30% vs. 70%, P<0.01). Secondary outcomes and adverse effects did not differ between the two groups. Gharehbaghi(21) studied 50 infants between 33 and 37 weeks' gestation, and birth weight ≥1800 g, treated with surfactant for RDS. Clinical outcomes were similar in the two groups, with 4% of supraglottic airway infants and 16% of INSURE infants receiving MV after surfactant (P=0.16). One RCT compared the use of supraglottic airway surfactant and intubation with continued MV in 48 infants of 28-35 weeks' gestation and ≥1000 g at birth.(25) Of the 26 infants in the supraglottic airway group, 46% received MV, while all infants in the control group received MV as per the trial protocol. Other clinical outcomes were similar in both groups. Surfactant administration with continued MV was not the recommended approach in either of the last two European RDS guidelines (which suggest INSURE, or more recently MIST, provided clinicians are skilled in this technique),(2, 26) so this study is less relevant to current practice.

2.2.3 Results of Pooled Analyses

A recent systematic review and meta-analysis(27) included five of the above RCTs and found supraglottic airway surfactant administration to be associated with a reduction in MV in comparison with both continued CPAP (risk ratio [RR] 0.57, 95% confidence intervals [CI] 0.38 to 0.85), and with surfactant administration via endotracheal tube (RR 0.43, 95% CI 0.31 to 0.61). However, the authors cautioned that these findings were based on a limited number of enrolled infants in studies of varying quality, with some being ceased earlier than planned, and classed the evidence as of very low quality. They recommended that current use of surfactant administration via supraglottic airway be limited to clinical trials.

2.2.4 Summary

In summary, there are three RCTs, totalling 180 infants, comparing supraglottic airway surfactant administration with laryngoscopy approaches targeted at avoiding MV, all of which utilised INSURE. There are no published RCTs comparing supraglottic airway surfactant administration with MIST, the current recommended standard.(2)

2.3 Considerations in Trial Protocol Development

2.3.1 Eligibility

As surfactant is a treatment for RDS, infants will be eligible if they meet clinical criteria consistent with that diagnosis, specifically that they are preterm (<37 weeks' gestation at birth), and have FiO_2 requirement consistent with the recommended threshold for surfactant treatment in consensus guidelines (≥0.30). The diagnosis of RDS will be confirmed with chest x-ray or lung ultrasound prior to enrolment, except where surfactant treatment is required urgently and would be delayed by imaging. Although surfactant is most

frequently administered within the first 24 hours of life, data from MCH and RWH indicate that 30% of MIST-treated infants received their first dose at 24-48 hours, so an age limit of 48 hours has been specified.
Currently available supraglottic airway devices have been used in infants as small as approx. 800g. However, the majority of infants in published work are ≥1250g, and the procedure is likely to be more challenging in smaller infants due to the physical dimensions of the device, so 1250g was chosen as the lower weight limit. Although gestational age is more commonly used to define eligibility limits in trials including preterm infants, birth weight can vary substantially in a population at a given gestation: for example, at 30 weeks, the 10th and 90th centiles for male infants are approx. 1000 and 1750 g respectively. Given the physical limitations on the feasibility of device insertion in smaller infants, a lower weight limit is more appropriate in this trial.

2.3.2 Treatment Approach

The approach to the intervention treatment in this trial is largely informed by the experience of the investigators based at The Royal Hospital for Sick Children, Glasgow, who have treated approximately 80 infants with supraglottic airway surfactant. They conducted a detailed audit of the first 60 infants,(28) of whom the smallest was 1200g and 13/60 were <1500g. The procedure was performed successfully in all 60 infants with eventual need for intubation in 10/60 (17%). This approach aims to administer the surfactant whilst the infant is breathing spontaneously and receiving CPAP via the supraglottic airway, with the option of providing positive pressure ventilation via the supraglottic airway if there is apnoea unresponsive to stimulation. Therefore, the intended method of surfactant distribution into the lungs in both the intervention and control groups is by negative pressure inspiration, during spontaneous breathing. In the intervention group, a surfactant giving tube is inserted via a duckbill port in the circuit to 16cm, to reach the distal end of the airway device, allowing simultaneous provision of respiratory support and surfactant administration. Sedation is not routinely required, but we have specified the use of atropine pre-medication in both treatment groups as this was associated with reduced occurrence of bradycardia during MIST at MCH and RWH.(29)
Repeat surfactant administration by any route will fulfil primary outcome failure criteria. Infants allocated to the MIST group may not receive supraglottic airway surfactant. However, infants allocated to the supraglottic airway surfactant group may receive the second dose of surfactant by either supraglottic airway or MIST, as per the treating clinician. Although there is no clear evidence that supraglottic airway surfactant is less effective than MIST, this is consistent with the non-inferiority trial design and use of 'rescue' standard treatment as described in previous trials.(5, 30) Although our data indicate that (if required) repeat surfactant is typically administered within 24 hours of the first dose in approx. 80% of infants, a period of 72 hours has been allowed as it will occasionally be administered later, this also ensures a consistent time period for ascertainment of both components of the primary outcome.

2.3.3 Setting

This study will be conducted in units currently using MIST in routine care (typically NICUs or advanced SCNs), with the aim of determining whether supraglottic airway surfactant is non-inferior to MIST. The SURFSUP Trial will

determine whether supraglottic airway surfactant is safe, effective, and feasible in both the NICU and SCN setting.

3 Aim/Hypotheses

3.1 Aim

We aim to evaluate the effectiveness and safety of surfactant administration via supraglottic airway, compared with MIST, in preterm infants with RDS in neonatal units.

3.2 Hypotheses

3.2.1 Primary Hypothesis

We hypothesise that surfactant administration via supraglottic airway will be non-inferior to MIST in preventing need for mechanical ventilation or repeat surfactant treatment within 72 hours of randomisation, in preterm infants with RDS.

3.2.2 Secondary Hypotheses

We hypothesise that compared with MIST, surfactant administration via supraglottic airway will:

- Result in a lower rate of physiological instability, assessed by incidence of bradycardia and desaturation
- Result in no difference in adverse events
- Be easier to perform for treating clinicians

4 Outcomes

4.1 Primary Outcome

The primary outcome of the trial is the rate of mechanical ventilation or repeat surfactant within 72 hours of randomisation.

4.2 Secondary Outcomes

Secondary outcomes include, but are not limited to:

4.2.1 Procedural Outcomes

1. Incidence of bradycardia <100 bpm during the procedure
2. Desaturation during procedure to SpO_2 <80% (including lowest SpO_2, duration of desaturation <80%)
3. Clinician satisfaction with procedure (survey)
4. Number of attempts to complete the procedure (one attempt is any insertion of laryngoscope or supraglottic airway into the mouth, regardless of whether surfactant is administered)
5. Total duration of procedure (time from first device insertion to final device removal; in the MIST group this is time from first insertion of either laryngoscope or catheter to final removal of both devices)

4.2.2 Clinical Outcomes

1. Number of surfactant doses, and total dose received in mg/kg
2. Mechanical ventilation at any time during admission
3. Reason for intubation and mechanical ventilation
4. Duration of respiratory support in total and by type (e.g. MV, CPAP, nHF)
5. Post-menstrual age at last day of supplemental oxygen use
6. Receipt of respiratory support or oxygen at 36 weeks' postmenstrual age (for infants born at <32 weeks' gestation only)
7. Pneumothorax requiring treatment (needle aspiration or chest drain)
8. Death before neonatal unit (NICU/SCN) discharge
9. Intraventricular haemorrhage (and Papile grade) or cystic brain injury (for those infants receiving neuroimaging according to standard unit guidelines)
10. Age in days at time intravenous fluids first ceased
11. Duration of hospital admission

5 Population

5.1 Eligibility Criteria

Infants are eligible for inclusion in the trial if they meet **all** of the following criteria:

- Born preterm at <37 weeks' gestation
- Birth weight ≥1250 g
- Age <48 hours
- Diagnosis of RDS, confirmed with chest x-ray or lung ultrasound, except where surfactant treatment is required urgently and would be delayed by imaging
- FiO_2 ≥0.30 to maintain target SpO_2, on non-invasive respiratory support (CPAP/NIPPV or nHF)

5.2 Exclusion Criteria

Infants are excluded if they meet **any** of the following criteria:

- Previous treatment with surfactant or mechanical ventilation via an endotracheal tube
- Urgent need for intubation and mechanical ventilation as determined by the treating clinician
- Known pneumothorax
- Major congenital anomaly of lungs, heart, or airway
- Not receiving full active intensive care (i.e. palliative/comfort care)

6 Recruitment and Consent

Prospective informed parental consent is required prior to enrollment in the study. The study team will approach the parent(s) of infants meeting the eligibility criteria (or likely to meet the eligibility criteria) on the advice of the treating clinical team. The study team member will provide a verbal and written explanation of the trial (see PICF) and take consent from the parent(s). The parent(s) will be able to consider their decision up until the clinical team deems

that administration of surfactant treatment is necessary, at which time the infant will receive standard care if consent has not been provided.
All parents present at the recruiting centre will be approached for written consent, using the trial PICF.
For parents who are not present at the recruiting centre (e.g., when the infant has been born at an external hospital and transferred to the recruiting centre for ongoing care), a two-stage consent process will be used to ensure these families are offered the opportunity to participate:
1) Oral assent will be taken by telephone, using the trial oral assent form.
2) Written consent, using the trial PICF, will then be confirmed at the earliest reasonable opportunity when the parents are present at the recruiting site.
In this circumstance, randomisation and treatment allocation will occur after oral assent has been given. Written confirmation of consent is required for the infant and their data to remain in the trial in all cases. The right of the parents to withdraw from the trial at any time is preserved.
Variations in the consent procedure may be required at international sites (e.g., due to language or local ethical guidelines). However, in all centres, informed parental consent will be required for participation, and recruitment will be consistent with ICH Good Clinical Practice guidance, and the conditions applied by the HREC responsible for study oversight.

7 Randomisation

A computerised random number generator will be used allocate infants to a treatment group, using random permuted blocks with different block sizes. Randomisation will be pre-stratified by centre and birth weight (<1500 g, and ≥1500 g). The REDCap electronic randomisation tool will be used to ensure that infants meeting eligibility and consent criteria can be quickly randomised to receive their allocated surfactant treatment.

8 Allocated Treatment

8.1 Pre-Procedure

- In both treatment groups, airway instrumentation will be performed by a neonatal clinician (doctor or nurse practitioner) appropriately trained in airway management, including both MIST and supraglottic airway placement
- The clinician to perform airway instrumentation will be assigned by the clinical team prior to randomisation taking place to prevent bias, so must be appropriately trained to provide both treatment methods
- A second clinician (medical or nursing), appropriately trained in surfactant administration, will be identified to assist with surfactant administration
- Appropriate equipment for resuscitation, including endotracheal intubation and ventilation, will be available to the clinical team in the event that this is necessary
- All infants will receive continuous monitoring of oximetry and heart rate during surfactant administration

- All infants will have intravenous access in place prior to surfactant administration
- Aspiration of stomach contents via gastric tube will be performed prior to the procedure in all infants
- Caffeine is not expected to be routinely prescribed in this population (birth weight ≥1250 g), but is recommended for infants born <30 weeks' gestation and should always be administered prior to surfactant treatment in any infant who has exhibited signs of apnoea
- Atropine IV (dose as per centre protocol) will be administered to all infants immediately prior to surfactant administration, in both treatment groups. In the event that a participating centre does not wish to use atropine premedication, this must apply for all included infants, and in both treatment groups
- Supraglottic airway surfactant infants will receive no sedative or muscle relaxant pre-medication
- Use of any sedative or muscle relaxant pre-medication in the control group will be according to local unit guidance
- Oral sucrose will be used for pre- and post-procedure analgesia in both treatment groups according to centre protocols
- Surfactant will be prescribed at a dose of 200mg/kg for the first dose and as per standard treating unit guidance for any subsequent doses
- A GoPro camera will be positioned to include the infant, and monitor display of oximetry and heart rate, within the field of view

8.2 Intervention Group (Supraglottic Airway Surfactant)

- This is described in detail in the trial document "Supraglottic Airway Surfactant Procedure", attached at the end of this document as an appendix.

8.3 Control Group (Surfactant via Direct Laryngoscopy)

- Surfactant administration by MIST in the control group will be carried out as per standard clinical guidance in the participating centre
- Pre-medication will be as per standard clinical guidance in the treating centre, with the exception of sucrose, which is mandatory as above. Use of atropine pre-medication will be consistent in both the intervention and control groups in a given study centre (either all receive atropine, or all do not receive atropine)

8.4 Post-procedure Management (Both Treatment Groups)

- A second dose of surfactant (dose and timing as per standard treating unit policy) by the allocated treatment method may be given within the 72 hours after randomisation, if required FiO_2 is ≥0.30. If this occurs, the primary outcome criterion is fulfilled.
- At the discretion of the treating clinical team, repeat surfactant may be given by MIST in the supraglottic airway group. **Use of supraglottic airway for repeat surfactant in the MIST group is not permitted**
- The need for mechanical ventilation will ultimately be at the discretion of the treating clinical team. However, recommended intubation criteria are receipt of maximal non-invasive respiratory support (as per local guidance) and any of:

    - Required FiO2 ≥0.40 to maintain target SpO_2 as per unit guidelines
    - Respiratory acidosis with pH<7.20 and pCO2 >65 on blood gas analysis
    - Severe or worsening apnoea
- Reason for intubation and mechanical ventilation, and the FiO2 and blood gas analysis values prior to intubation, will be recorded in the CRF
- Mechanically ventilated infants may receive further surfactant by endotracheal tube at the discretion of the treating clinical team
- 'Respiratory support' in this trial is defined as any of MV, NCPAP/NIPPV, or nHF at set flow ≥4 Litres/min
- Management of non-invasive respiratory support (e.g. escalation, weaning, and cessation) will be as per standard unit guidance in both groups

9 Training

The approach to training prior to trial commencement will be at the discretion of the clinical team at each centre, and will be adjusted depending on local experience and requirements. For example:

- Clinicians at The Royal Hospital for Sick Children, Glasgow have substantial experience in this technique as part of standard clinical care therefore no additional training in this method will be required at their centre. The Supraglottic Airway Surfactant Procedure for this trial is based on the approach they have used successfully in approx. 80 infants.
- Monash Newborn staff are routinely trained in supraglottic airway insertion. However, supraglottic airways are not currently used to administer surfactant. At Monash Newborn, training sessions including the use of a neonatal manikin will be conducted. At the two Melbourne centres, the study will commence as a pilot trial of 10 infants, and the procedural outcomes will be reported to the HREC prior to commencing the full randomized trial at these sites.

10 Statistical Analysis and Sample Size

10.1 Sample Size Calculation

The trial will assess the rate of mechanical ventilation or repeat surfactant treatment within 72 hours of randomisation. Our audit indicates that for infants meeting the eligibility criteria for this trial, 76% of those treated with MIST successfully avoid the primary outcome, mechanical ventilation or repeat surfactant treatment within 72 hours. We will assess whether supraglottic airway surfactant administration is non-inferior to surfactant administration by MIST, with a non-inferiority margin of 9%, i.e., an absolute increase from 24% primary outcome rate in the control group to 33% in the intervention group. If both the point estimate and upper 95% confidence interval fall within an absolute difference of 9%, the criteria for non-inferiority will be met. If there is truly no difference in efficacy between groups, then 474 infants per group will be required, with 90% power and a two-sided 95% confidence interval, to demonstrate non-inferiority with a margin of 10%. To allow for a small

proportion of exclusions (≤5%) from per-protocol analysis, we will recruit 500 infants per group: a total of 1000 infants.

10.2 Projected Recruitment

We anticipate that the initial participating centres (MCH and RWH in Melbourne, the Royal Hospital for Sick Children and Wishaw General Hospital in Scotland) will provide approximately 110 eligible infants per year. We aim to extend the trial to 10-15 centres, which we project will allow completion of recruitment within five years.

10.3 Statistical Analysis Methods

The incidence of the primary outcome will be compared using risk difference and 95% confidence interval (CI). Dichotomous secondary outcomes will be compared using risk difference and 95% CI, and continuous secondary outcomes using a t-test or Wilcoxon rank sum test as appropriate. Primary analyses will be by intention-to-treat. A *per protocol* analysis will be conducted for the primary outcome and for the rate of mechanical ventilation within 72 hours. Infants will be excluded from the *per protocol* analysis for the following reasons:

- Allocated intervention not received
- Enrolled despite not meeting eligibility criteria
- Other major protocol deviation(s) occurring prior to determination of the primary outcome

Subgroup analyses of the primary outcome and component elements will be conducted for the two gestational age strata. A detailed statistical analysis plan will be completed prior to the initiation of data analysis, at completion of recruitment to the trial.

11 Data Management

11.1 Data Collection

An electronic case report form (CRF) will be created in a REDCap database, to allow data entry by the study investigators. A video recording of the infant will be used to allow determination or confirmation of procedure data by the research team.

11.2 Procedure Data

Procedure data will include the outcomes stated in section 4.2.1 above.

11.3 Clinical Outcome Data

Clinical outcome data will include the outcomes stated in section 4.2.2 above.

11.4 Demographic Data

Demographic data include, but are not limited to, the following:

1. Birth weight in grams
2. GA in weeks + days at birth
3. Age at randomisation in hours
4. Mode of birth
5. Sex
6. Multiple birth

7. Maternal antenatal corticosteroid treatment <7 days prior to birth
8. Maternal gestational diabetes

11.5 Data Storage

Data will be stored in re-identifiable form. A paper log will be maintained at each study centre, including identification of participants. All paper records will be stored in locked filing cabinets accessible only to study investigators. Each participant will be allocated a unique study number, allowing de-identification of data prior to entry in the secure electronic REDCap database. Access to the database will be limited to study investigators, and will be password-protected. Video recordings of the procedure will be stored on password-protected computers at each study site, and will be accessible only to study investigators, unless specific additional written consent for use in education or presentations has been provided by the parents. Data will be stored until the 25th birthday of the youngest participant, as per the Victorian Health Records Act (2001), and in accordance with local regulations at any study site outside Victoria.

12 Adverse Events

12.1 Adverse Events

Adverse events (AEs) are defined as follows:

1. Bradycardia <100bpm (of any duration) during surfactant administration
2. Desaturation <80% lasting 30 seconds or more (during a single event) during surfactant administration

Audit data from MCH and RWH indicates that in the control group, we can expect bradycardia <100 bpm to occur in approximately 14% of infants and desaturation <80% lasting 30 seconds or more to occur in approximately 43% of infants.

12.2 Serious Adverse Events

Serious adverse events (SAEs) are defined as follows:

1. Death within 72 hours of randomisation
2. Need for cardiopulmonary resuscitation (chest compressions) within one hour of surfactant treatment
3. Pneumothorax requiring drainage (needle aspiration or intercostal catheter insertion) within 24 hours of randomisation

SAEs must be reported to the trial CPI and reviewing HREC within 72 hours of detection by the research team.

13 Study Oversight

13.1 Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) was established prior to the commencement of the trial. The DSMC consists of at least two independent neonatologists/paediatricians and an independent statistician. Members are noted on page 2.

The DSMC will conduct a review of AE and SAE rates after the primary outcome has been determined for 50, 100, and 500 infants (50% recruitment). The DSMC

may recommend re-evaluation of trial conduct, or complete cessation of the trial if there is a statistically significant increase in SAEs in the intervention group, or other significant safety concerns. Additional reviews of SAEs and AEs may be scheduled at the discretion of the DSMC. The DSMC will also consider feasibility of trial completion based on recruitment progress, adherence to the trial protocol, and any new evidence that may make continuing the trial unethical. A formal terms of reference document will be created in consultation with the DSMC after their appointment.

14 Trial Registration

The trial will be registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) prior to recruitment of the first participant.

15 Funding

Initial recruitment to the trial in the two Australian centres (MCH and RWH) will begin using funding available from a related NHMRC Project Grant (1098790), research support funding from the CPI's NHMRC Investigator Grant (1175364), funding secured by the Cis from the CRE in Newborn Medicine, and a University of Melbourne Innovation Grant (CI Owen). Further funding will be sought to support expansion to other recruiting centres and completion of the trial, including an application to the NHMRC Clinical Trials and Cohort Studies scheme.

16 Dissemination of Results

The study findings will be presented at national and international conferences, and published in peer-reviewed medical journals.

17 Acknowledgement

We acknowledge the work of Dr Joyce O'Shea and Dr Natalie Smee in devising the approach described in the "Supraglottic Airway Surfactant Procedure".

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19 Appendix 1: Supraglottic Airway Surfactant Procedure

Equipment List

- T-piece circuit with duckbill port
- Size 1 i-gel supraglottic airway
- Lubricant gel
- Syringe and surfactant giving tube (e.g. gastric tube)
- Colorimetric CO_2 detector (e.g. Pedicap)
- Blunt needle (to probe duckbill port for patency)
- Pulse oximeter
- GoPro camera

Pre-Procedure

Ensure preparation for procedure as per Section 8.1 of Trial Protocol:

- Surfactant prescribed, checked and drawn into syringe with gastric tube
- Equipment for resuscitation, face mask ventilation, intubation available
- T-piece circuit with duckbill port connected and settings checked (PIP, PEEP, FiO_2) as per clinical team. Patency of port checked with gastric tube or blunt needle
- Oximetry and heart rate monitoring in place
- Aspirate stomach and **remove pre-existing gastric tube**
- GoPro camera positioned to include infant and monitoring in field of view and recording started

Premedication

- Sucrose PO – for analgesia
- Atropine IV (if applicable) – administer immediately prior to procedure, dose as per unit guidance

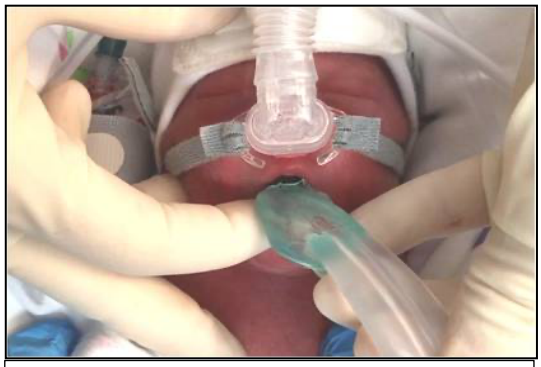
Inserting the I-Gel

- Nasal CPAP interface should be left in place throughout the procedure, unless removal is required to secure correct position of i-gel
- Lubricate the back and sides of the i-gel
- Tilt the infant's head back slightly, open the mouth and apply jaw thrust
- Insert the tip of the i-gel along the hard palate with the open side facing the tongue
- Continue inserting the i-gel along the posterior pharyngeal wall. Resistance is felt when the i-gel tip sits on the oesophagus
- The opening of the mask should cover the entrance to the larynx (see image).
- In some infants, a tongue depressor/laryngoscope may be required to maintain tongue position while inserting the i-gel.
- Confirm correct placement by attaching circuit and Pedicap to i-gel

Surfactant Administration

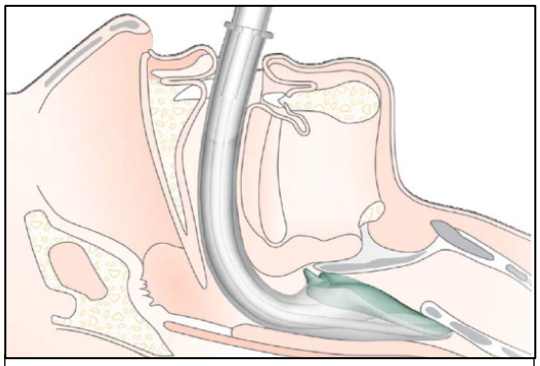
- Surfactant catheter inserted to 16cm by assistant, to reach distal end of i-gel, whilst clinician maintains i-gel position
- Administer surfactant in small aliquots over approx. 2 minutes, during spontaneous breathing with continued CPAP via supraglottic airway
- If apnoea, desaturation or bradycardia occur, pause administration and provide stimulation and/or IPPV if required
- On completion and removal of i-gel, ensure nasal CPAP in correct position

1. Lubricate back and sides of i-gel

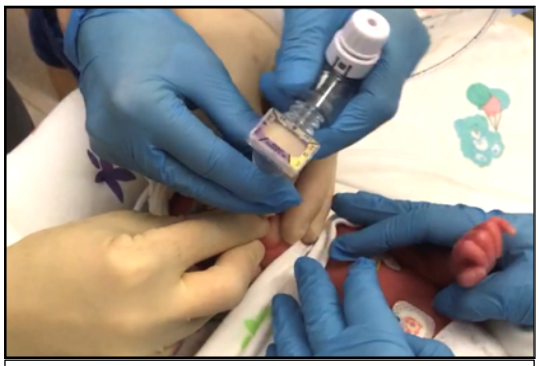


2. Insert i-gel along hard palate, over tongue

3. Stop when resistance felt, hold in place



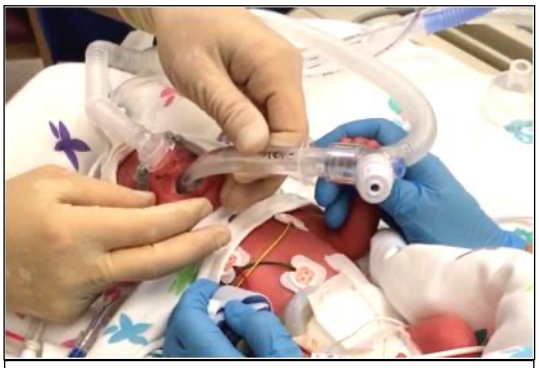
4. Target final position of i-gel over airway



5. Attach Pedicap and circuit to confirm position, adjust if needed

6. Remove Pedicap, insert giving tube to 16 cm via duckbill port

7. Administer surfactant over 2-3 minutes, encouraging breathing



8. Remove i-gel, ensuring nasal CPAP in correct position