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Multicentre, randomised trial of preterm infants receiving caffeine and less invasive surfactant administration compared with caffeine and early continuous positive airway pressure (CaLI trial): study protocol

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ABSTRACT

Introduction Respiratory distress syndrome (RDS) or surfactant deficiency occurs primarily in premature infants resulting in composite outcomes of death or bronchopulmonary dysplasia. Initial management strategies for preterm infants with RDS includes early initiation of continuous positive airway pressure (CPAP) and titration of fractional inspired oxygen (FiO_2), and may include the use of less invasive surfactant administration (LISA) to avoid the need for mechanical ventilation. In order to optimise success of non-invasive support, the use of early caffeine therapy may be critical to the success of LISA. The objective of our trial is to evaluate whether infants that receive early caffeine, CPAP and surfactant via the LISA method compared with infants that receive caffeine and CPAP alone, have a decreased need for invasive mechanical ventilation in the first 72 hours of life.

Methods and analysis CaLI is an unblinded multicentre, randomised controlled, trial of 180 preterm infants (24+0–29+6 weeks corrected GA). Criteria for intubation/treatment failure will follow guidelines for the management of RDS, including: (1) CPAP level of 6–8 cmH20 and FiO_2 >0.40 required to maintain saturations 90%–95% for 2 hours after randomisation; (2) a pH of 7.15 or less or a $paCO_2$ >65 mm Hg on any (2) blood gases (arterial/capillary/or venous) at least 2 hours after randomisation and in the first 72 hours of life; (3) continued apnoea/bradycardia/desaturation events despite nasal intermittent minute ventilation mode of ventilation. Infants will be randomised by 1 hour of life and caffeine/LISA treatments administered by 2 hour of life. Caffeine will be administered prior to surfactant in the LISA arm and before 2 hours of life in the control arm.

Ethics and dissemination Chiesi Farmaceutici, S.p.A is the sponsor of CaLI. Ethical approval has been obtained. Results will be submitted for publication in peer reviewed journals.

Trial registration number www.Clinicaltrials.gov: NCT04209946; Pre-results.

Strengths and limitations of this study

- Limited power for longer-term outcomes such as bronchopulmonary dysplasia and neurodevelopmental impairment due its smaller size.
- CaLI is not a double-blind trial due to the complexity of blinding treatments in the delivery room with different modes of administration and the need to initiate the trial very rapidly after birth.
- The trial is the first to be prescriptive in the use of caffeine as a cointervention for less invasive surfactant administration (LISA) to test its benefit.
- This study will be the first re-evaluate the use of early surfactant with the LISA method compared with expectant management with continuous positive airway pressure alone.

INTRODUCTION

Premature infants are commonly born with respiratory distress syndrome (RDS) or surfactant deficiency that may lead to respiratory failure. Advances in respiratory management include, early initiation of continuous positive airway pressure (CPAP) and titration of fractional inspired oxygen (FiO_2),[1] modifications in the administration of surfactant therapy using less invasive techniques, and the avoidance of mechanical ventilation.[2] Another strategy to optimise success of non-invasive support involves the use of caffeine therapy to serve as a respiratory stimulant. Dekker *et al*[3] demonstrated that the administration of caffeine in the delivery room compared with on admission to the neonatal intensive care unit (NICU) produced greater minute ventilation and tidal volumes in premature infants <30 weeks. The less invasive surfactant

administration (LISA) to spontaneously breathing preterm infants has been reported to reduce the need for mechanical ventilation.[4] A recent meta-analysis of non-invasive ventilation strategies demonstrated that LISA had the lowest odds ratio (OR, 0.49; 95% CI 0.3 to 0.79) for the development of the composite outcome of death or bronchopulmonary dysplasia (BPD) among non-invasive ventilation strategies compared with invasive mechanical ventilation.[5] The combination of early caffeine and LISA has not been tested and despite these results and studies showing a decreased need for invasive mechanical ventilation compared with CPAP and the use of the LISA method remain limited.[6 7]

METHODS AND ANALYSIS

The study is designed as a multicentre, unblinded, randomised trial of preterm infants receiving caffeine and LISA compared with caffeine and CPAP with a primary outcome of frequency of endotracheal intubation between the two groups (caffeine and LISA vs caffeine and CPAP) within the first 72 hours of life. The study will be conducted at three sites in the USA (Loma Linda University Medical Center, University of California, Irvine, and Sharp Mary Birch Hospital for Women & Newborns) over a 3-year period. The following variables will be collected:

1. Frequency of subjects requiring endotracheal intubation between the two groups (LISA vs CPAP) in the first 72 hours of life.
2. Duration of mechanical ventilation and/or CPAP.
3. Requirement of supplemental oxygen at 36 weeks corrected age.
4. Grade III and IV intraventricular haemorrhage (IVH).
5. Spontaneous intestinal perforation.
6. Necrotising Enterocolitis (NEC).
7. Retinopathy of prematurity (ROP) requiring surgery.
8. Need for repeat surfactant dosing.
9. Long-term neurodevelopmental data through 2 years of age.

Pregnant women will be identified and screened from the labour and delivery floor or perinatal special care unit at each site. Parents will be approached and consented prior to delivery. In the delivery room, after the infant's first 5 minutes of life, the research staff or neonatal delivery team will open the randomisation envelope for the proper gestational age (GA) group. Multiples will be randomised to the same treatment group for ease of consent and family considerations. There is no crossover allowed between the LISA and CPAP groups, subjects should receive their randomised treatment. If the physician determines that the infant requires intubation or is determined to be unstable, the infant will be intubated and excluded from the study.

Inclusion criteria

- Premature infants born at 24–29+6 weeks GA.
- Informed consent obtained (antenatal).
- Infant is spontaneously breathing on CPAP of 5–8 cm H20 with an FiO_2 of <0.40 and maintains a normal heart rate (HR >100 bpm).

Exclusion criteria

- Declined consent.
- Infants with known congenital anomalies.
- Unstable immediately after birth, requiring intubation in the delivery room.

All infants found to have anomalies postrandomisation will be analysed by intention-to-treat principle.

Patient allocation

Randomisation cards are computer generated by Sharp Mary Birch Hospital for Women and Newborns and will solely be known by the data manager. Each randomisation card contains group assignment, real-time data information, and a randomisation number sealed in an opaque envelope with a label that indicates the envelope sequence number, site (facility) number, and stratification by GA. These envelopes will be logged by the data manager in a secured data file and then distributed to each research facility. We will enroll 180 preterm infants and will stratify by GA (24–26+6 weeks and 27+0–29+6 weeks), labelled as such on opaque envelopes.

Randomisation

In order to allow for initial stabilisation on CPAP, infants will be randomised by 1 hour of life. Consented infants that are assessed by a provider as clinically stable (ie, HR >100 bpm) and spontaneously breathing on CPAP (5–8 cm H_2O) will be randomised. Stabilisation of premature infants at delivery may include stimulation, positive pressure ventilation (PPV) or CPAP. Only spontaneously breathing infants on CPAP, maintaining normal HR and saturations will be included and randomised. When the neonatal provider assesses the infant to be stable on CPAP, a member of the research or neonatal team will pull a randomisation card according to the infant's corrected GA. Once the treatment group is identified (caffeine and LISA or Caffeine and CPAP), intervention will begin based on allocation (see below).

LISA group

For infants randomised to LISA, intravenous access will be established to administer caffeine. An orogastric tube will be placed into the stomach prior to laryngoscopy and the contents aspirated before and after the procedure to document any oesophageal surfactant administration. A thin catheter (16G angiocatheter) will be measured and the depth of insertion will be marked with intubation tape. The catheter will then be placed in the trachea under direct or videolaryngoscopy by a neonatal practitioner. After the catheter is placed, the laryngoscope will be removed, the angiocatheter held securely in place, and the infant will remain on CPAP. Surfactant (Curosurf 2.5 mL/kg, based on estimated fetal weight) will be slowly administered over 1–2 min (approximately in three aliquots) assuring synchronised instillation with infant's

breathing pattern while on CPAP. After instillation, the catheter will be removed and CPAP will continue. If apnoea occurs during or after the procedure, PPV will be initiated. To improve adherence to protocol interventions, all sites have agreed on using senior level physicians or neonatal practitioners that have prior experience with LISA.

Data collection in the LISA group is collected using the caffeine and LISA Randomisation card (online supplemental file 1).

CPAP group

Infants randomised to early CPAP will be managed according to subsite unit practice for preterm infants on CPAP. If randomised to the CPAP group, intravenous access will be established to administer caffeine and the infant will continue on CPAP unless infant meets failure criteria and requires intubation.

Data collection in the CPAP group is collected using the caffeine and CPAP randomisation card (online supplemental file 2).

Caffeine

Caffeine will be given in both groups as soon as intravenous access is obtained. Since caffeine must be given prior to the LISA procedure it must be given as early as possible and before 2 hours of life. Similarly, if randomised to CPAP, caffeine will be given before 2 hours of life. If infants in the CPAP group meet intubation criteria, and the loading dose of caffeine has not been administered, to avoid any delay in intubation, caffeine will be given no later than thirty minutes after intubation.

The caffeine preparation for this study is caffeine citrate with a loading dose of 20 mg/kg given via an intravenous access over 15–30 min. Time of caffeine administration will be captured in subject's electronic medical records (EMR).

Blinding

Due to the nature of the intervention, neither participants nor staff can be blinded to allocation, but are strongly encouraged not to disclose the allocation status of the participant at the follow-up assessments.

A separate research team would not always be available for randomisation. Therefore, the clinical team caring for the infant will follow strict guidelines for intubation and management of infants to reduce any post randomisation bias (see below).

Intubation criteria

As an unblinded trial, it is critical that both groups are standardised to avoid bias towards one arm for mechanical ventilation/treatment failure. Therefore, strict delivery room/NICU criteria will be used. Furthermore, infants cannot be randomised until clinically stable to ensure that unstable infants that cannot be transitioned on CPAP would not be included. These would include infants that need intubation as specified in the Neonatal Resuscitation Programme (NRP) guidelines, such as: (1) when chest compressions are needed; (2) ineffective ventilation (inability to obtain good chest rise and fall despite implementation of the corrective ventilation steps: mask adjustment; reposition airway (try again); suction mouth and nose; open mouth (try again); pressure increase (up to 40 cm H_20 pressure); use of an airway alternative, as indicated by the NRP guidelines to obtain effective ventilation; (3) prolonged PPV (infants requiring PPV for more than 2 min in order to maintain HR >100 bpM) ; or (4) prolonged hypoxia (preductal SpO_2 is not met despite 100% supplemental oxygen and resuscitation interventions). Randomisation should be delayed until the providers are comfortable that none of these criteria are met in order to avoid any early selection bias.

After stabilisation on CPAP, infants can be randomised. Criteria for intubation/treatment failure will be recent guidelines for the management of RDS,[1] including: (1) CPAP level of 6–8 cm H_20 and FiO_2 >0.40 required to maintain saturations 90%–95% for 2 hour after randomisation; (2) a pH of 7.15 or less or a $paCO_2$ >65 mm Hg on any (2) blood gases (arterial/capillary/or venous) at least 2 hours after randomisation and in the first 72 hours of life; (3) continued apnoea/bradycardia/desaturation events despite nasal intermittent minute ventilation (NIMV) mode of ventilation. To avoid the bias of avoiding intubation since the study is not masked, infants with these criteria will be regarded as treatment failures.

Sites will use their standard approach for non-invasive ventilation as they have agreed to use each mode (nasal continuous positive airway pressure or NIMV) equally regardless of randomisation. Subsequent analysis will include primary mode of non-invasive ventilation.

Data collection on intubation will be collected using the Intubation card (online supplemental file 3).

Participant timeline

To indicate participant timeline between the caffeine and LISA procedure versus the caffeine and CPAP procedure, the CaLI Study Overview Diagram (online supplemental appendix 1) is attached.

Patient and public involvement

We have collaborated with parents by presenting this study to the Sharp Mary Birch Parent Advisory Board. Based on their experiences and preferences, we have incorporated their suggestions and they enthusiastically support the study. One of the parents has agreed to be on the data safety monitoring board (DSMB) to monitor the trial for safety. Their involvement includes input on the consent form and perspective on recruitment of families.

Study overview diagram:

Data management and collection

Data will be managed using Research Electronic Data Capture (REDCap) tools hosted and managed at Sharp Mary Birch Hospital for Women & Newborns (online supplemental file 4). All collected variables are listed in the data report form: LISA Data Collection (online

supplemental file 1), CPAP arm Delivery Room Data Collection (online supplemental file 2) and CaLI Intubation Data Collection (online supplemental file 3). Loma Linda University Medical Center, University of California Irvine Medical Center, and Sharp Mary Birch Hospital for Women & Newborns have extensive experience with REDCap data entry.

Randomisation cards are also used as data collection forms, with pertinent information completed and signed by care providers in real time. To maintain integrity of the study data, site data coordinators will enter data information into REDCap and verified by the primary site data coordinator and research coordinator prior to locking the subject's electronic data file.

Data and safety monitoring plan

An independent, well recognised, DSMB with experience with respiratory trials is chosen for this study. Drs. Brad Yoder and Wally Carlo have led and participated in a number of trials studying topics including: High-Flow Nasal Cannula, High Frequency Ventilation, and Surfactant. In addition, a former parent (KN) that has participated in research trials has agreed to serve on the DSMB. The DSMB will: (1) oversee the safety data on all study patients, (2) safeguard the interests of all study patients, (3) monitor the overall conduct of the trial, (4) advise the investigators in order to protect the integrity of the trial and (5) supervise the conduct of all interim analyses. To this end, the DSMB will receive monthly reports from the trial on any injuries or adverse events (AEs), any developments that jeopardise the continued success of the trial, and data by which to accomplish the evaluation of predetermined early stopping rules. All serious AEs (SAEs), protocol deviations, non-SAEs and unanticipated problems (UPs) will be reported to the data coordinating centre (DCC) and forwarded to the DSMB if indicated (see below). Reports of AEs and recruitment will be sent monthly and demographics will be included with the interim and final safety and efficacy analyses. Interim analyses determined by the DSMB and the project statistician will be conducted independently from the trial leadership and staff. The definitions and reporting process are as follows:

SAEs defined as one or more of the following: decompensation during the administration of surfactant in either arm including the use of epinephrine in the delivery room and chest compressions, or death prior to discharge.

1. All SAEs will be reported within 72 hours of discovery of event, to the principal investigator (PI) and the site instututional review board (IRB).
2. Any Unexpected AE or serious deviation will be reported within 7 days of discovery of event to the DCC.

Non-serious events

Unexpected events that are non-serious are reported not more than 14 days after the PI first learns of the event. The DCC will forward all non-serious unexpected events to the DSMB, and main study PI. All other expected outcomes of prematurity, that is, BPD, IVH grades 1–4, ROP, NEC, will be collected in the electronic database and reviewed in interim reports. We have appointed a DSMB to work closely with the main study PI. There are no conflicts of interest with these individuals who are not research collaborators of, and are at separate institutions from the investigators at the enrolling sites.

The study will be closely monitored for issues of data quality, study conduct, and AEs. These analyses will be presented to the DSMB. Interim analyses will seek to identify results that are sufficiently extreme and precise, this is to offset the goal of obtaining additional data that might lead to more precise and perhaps less exaggerated and more convincing results, as well as information about differences in treatment effect by subgroups of patients. Determinations on stopping must reflect ethical considerations of the impact of interim results on clinical equipoise as well as considerations on the potential impact (or lack of impact) of interim results on clinical practice. The superiority must be tested in the context of this trial first and then superiority assessed, unless the DSMB is ethically motivated to stop the trial for superiority.

Statistical analysis plan

A chart review of the databases at Sharp Mary Birch Hospital for Women & Newborns demonstrated that 49% of our infants 24–29+6 weeks' gestation were intubated and mechanically ventilated in the first 72 hours of life after failing a trial of CPAP in the delivery room. A very conservative sample size calculation indicates that in order to detect a 22% absolute reduction (a reduction from 49% to 27%) we would need at least 75 subjects in each arm for an 80% power and a $p<0.05$ for significance. An adjustment of 1.12 derived from the NICHD Neonatal Research Network Generic Database, allowed for multiples to be randomised to the same treatment introducing a clustering effect.[8] In order to account for multiples and potential drop out of subjects we plan to consent 90 subjects in each arm (180 subjects total). A future detailed statistical analysis plan will be made available prior to completion of the trial.

Ethics and dissemination

Ethics approval has been obtained. Prior to any research procedure, consent will be obtained by the primary investigator or a delegated subinvestigator or a research associate. The mother or legally authorised representative must sign the informed consent document. Mother (or surrogate mother) must sign a Health Insurance Portability and Accountability Act (HIPAA) authorisation providing access to her medical records for collection of maternal data. Either mother, father, or legal guardian can sign a HIPAA authorisation providing access to the child's medical record for data collection purposes. The subject's legally authorised representatives will be given ample time to read the informed consent, ask questions of the research team, and discuss the study with their

family and/or the subject's physician. The informed consent process will be documented in the EMR and copies of the signed and dated consent will be given to the subject's representatives, placed in the subject's physical chart, and stored in a locked cabinet in the offices of the Neonatal Research Institute. Results will be published and presented at the Paediatric Academic Societies meeting on completion. Any important protocol modifications will be communicated to subsite lead investigators via secured email which will include automated confirmation of receipt and recorded audio/visual meetings.

Confidentiality

All data will be safeguarded in accordance with HIPAA and the principles and practices of strict confidentiality. Data will be maintained by numerical code rather than personal identifiers and computer-based files will be available only to persons involved in the study through the use of access privileges and passwords. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Protection against risk

Only research team members (with appropriate research training relevant to protection of human subjects) shall have access to the project's databases. The final trial data set will remain with the lead PI and DCC.

Appendix II

Informed consent form (online supplemental appendix 2).

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Contributors FI and ACK developed the initial protocol and manuscript. SH, KC, AH, AB, CU, NF and WR helped revise the manuscript and protocol. AM and JS helped develop the dataset and variables for the manuscript.

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Competing interests The principal investigator for the overall trial and each study site declare no financial or other competing interests.

Patient and public involvement statement Parents of former NICU patients were involved in the design of the protocol and consent.

Patient consent for publication Not required.

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