The LATTE Dosage Trial
Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial)

LATTE

Trial Handbook
Counties Manukau Health
Study Personnel
This study is coordinated by the Liggins Institute, University of Auckland

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Counties Manukau Health Main Contacts

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<thead>
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<tbody>
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<td>General research contact Ph: 021 897 982 <a href="mailto:latte@auckland.ac.nz">latte@auckland.ac.nz</a></td>
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<td></td>
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<td>Neonatal Pharmacist</td>
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Project Summary
Late preterm infants (34\textsuperscript{+0}-36\textsuperscript{+6} weeks’ gestational age (GA)) are the most common of all preterm infants, constituting 6% of all births or 3,700 births annually in New Zealand. These infants have a 30% increased risk of severe long-term neurodevelopmental impairment compared to infants born at term. While there has been progress in improving neurodevelopmental outcomes for infants born more preterm, it is only recently that late preterm infants have been recognised as being at risk of significant problems. Remarkably, there has been very little research on how to improve the long term outcomes of infants born late preterm.

In very preterm infants, both apnoea (pauses in breathing) and intermittent hypoxaemia (recurrent drops in oxygen saturation) are common and are associated with worse neurodevelopmental outcomes. Treatment with caffeine not only reduces apnoea and intermittent hypoxaemia in very preterm infants but also improves long-term neurodevelopment. While apnoea of prematurity is less common in late preterm infants, we have recently identified that infants born late preterm are also at increased risk of intermittent hypoxaemia. Caffeine has been shown to improve intermittent hypoxaemia in very preterm infants at 35 weeks’ and 36 weeks’ post-menstrual age, but there are no data to show if caffeine improves long-term neurodevelopmental outcomes in infants born late preterm.

The most effective dose of caffeine at this gestational age is uncertain. Very preterm infants have limited ability to metabolise caffeine, but this increases with greater gestational age. Therefore, late preterm infants are likely to need a higher dose of caffeine than very preterm infants. However, if the dose is too high it may have increased side effects and will not be tolerated. This randomised, placebo-controlled, dosage trial of prophylactic caffeine treatment will determine the most effective and best tolerated dose of caffeine to reduce intermittent hypoxia in late preterm infants

Eligibility Criteria

- Infants born between 34\textsuperscript{+0} – 36\textsuperscript{+6} weeks’ GA without contradiction to caffeine treatment.
- Randomised within 72 hours of birth

Exclusion criteria

- Major congenital abnormality
- Minor congenital abnormality likely to affect respiration, growth or development
- Previous caffeine treatment
- Renal or hepatic impairment
- Tachyarrhythmia
- Seizures
- Hypoxic ischaemic encephalopathy
- Residing outside of the Auckland DHB regions

Study Intervention
Infants will be assigned randomly by online randomisation to either caffeine citrate 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg or placebo, with 1:1:1:1:1 allocation, and stratified by study site and then for gestational age at birth (34, 35 or 36 weeks) (Figure 2). Infants will be randomised within 72 hours of birth. Infants from multiple births will be randomised to the same treatment group.
The staff member randomizing the infant will receive a study allocation letter (A to E or F to J) that corresponds to pre-labelled study bottles containing either caffeine citrate or water (identical appearance). Four different concentrations of the caffeine citrate (5 mg/ml, 10 mg/ml, 15 mg/ml and 20 mg/ml) will be used so that all infants receive the same dose volume (1 ml/kg, once daily), to maintain blinding.

The infant will be given a 2 ml/kg enteral loading dose of the study drug (10 mg/kg, 20 mg/kg, 30 mg/kg or 40 mg/kg of caffeine citrate or water) at 7-9 am on the first morning after the infant reaches 72 hours of age, followed by a daily dose of 1 ml/kg each morning (5 mg/kg, 10mg/kg, 15 mg/kg or 20 mg/kg of caffeine citrate or placebo) until until term equivalent age (40 weeks’ post-menstrual age). The dose will be recalculated for the infants’ weight gain weekly after the infant has regained birth weight.

The study drug is given via a nasogastric tube for infants with a tube in situ, and orally for infants who do not require a nasogastric tube. Infants who are not able to tolerate enteral medications will have the study drug withheld.

**Open Label Caffeine Citrate**

If an infant in the trial has apnoea or intermittent hypoxaemia clinicians will be encouraged to use oxygen or positive pressure ventilation (high flow or CPAP) as a first line treatment where appropriate. If necessary, clinicians can give a loading dose of caffeine citrate as an open label medication. If a clinician decides to continue caffeine treatment, they can discuss the option of partially un-blinding the infant (caffeine or placebo) with the Site Principal Investigator (see 2.2.4). Open label caffeine treatment will be recorded, and these infants will be included in the intention-to-treat analysis.

**Blinding/Unblinding**

**Blinding**

The research team and the infant’s parents will be blinded to treatment allocation. This will be achieved by dispensing caffeine in identical bottles with identical study drug solutions (caffeine and water).

**Emergency unblinding**

The infant may be un-blinded if judged clinically necessary by the clinical team caring for the infant, in agreement with the Site Principal Investigator. To unblind the infant’s study drug, the Site Principal Investigator will contact the Data Manager and ask them to contact the responsible clinician and/or hospital pharmacist with the study allocation. In the first instance this will be by partial unblinding (designated as either placebo or caffeine), unless the actual dose of study drug is required for the infant’s care. Please contact Dr Chris McKinlay in the first instance.
Obtaining Informed Consent

Once an eligible baby has been identified, one of the Research Team will approach mother/father and give them the Participant Information Sheet to read. Discuss the information with the mother (parents) and answer any questions she (they) may have. Allow time for mother (parents) to consider if they would like to participate in the study. If she (they) agree, complete the electronic consent form and explain what will happen next. If unable to obtain electronic consent, please use a hard copy and upload to the REDcap database.

Consent Documentation
- One copy will be electronically sent to parent(s)
- If baby is remaining in NNU as inpatient
  a) place a hard copy in the baby’s medical notes with a Participant Information Sheet
  b) place a ‘LATTE’ enrolment sticker within the clinical notes
  c) Place a ‘LATTE’ cot card on the bedspace

Randomisation

Randomisation will be completed by one of the Research Team staff. Randomisation can only occur once the baby has been screened and information entered into REDcap by research team.

Filepath: Paanui, KidzFirst, Neonatal Clinical Guidelines, Research Studies, Latte

- Scroll down to the Latte logo and click on it,
- click randomisation
- enter password: 249584MID

Health Professional notifications

After enrolment the research team will complete:

1. Electronic GP letter to advise of enrolment (available to view in Concerto)
2. Hospital wide alert on Concerto that baby has been enrolled into study
3. A printed enrolment letter to be placed in well-child book for LMC attention.
4. MCIS front page alert: Baby is a participant in the Latte Caffeine Dosage Trial.

Enrolment Data Information

The Research Team will collect from the mother:

- Demographic details, Antenatal & Neonatal information eCRF
- Smoking history & Caffeine Usage eCRF
- EPDS eCRF – see incidental findings SOP if raised
Pulse Oximetry: See SOP 2

Set up on NNU/Ward:
On the first night after randomisation, overnight oximeter monitoring within the unit is required for at least 12 hours. The Research Team will arrange for oximeter to be set up during the day.

Ensure that either the parents or the RN/RM on the ward are familiar with how to start the oximeter that evening and how to attach the sensor to baby – give laminated instructions.

Once baby is ready for overnight monitoring:
1. Check the power cable is plugged into the back of the machine and the wall socket and the plug is on at the wall. This is essential as the machine will initially run on battery power, but if this fails all data will be deleted and the recording will need repeating.
2. Make sure the cable is plugged in to the front of the machine and that the probe is attached to the cable
3. Turn on the oximeter (the screen will flash up initially with settings then go blank as it is set in sleep mode).
4. Apply the sensor to the baby’s right foot and secure with tape
5. Check that you see a red light emitting from the probe. This indicates the machine is on and working correctly.
6. Cover the probe with a sock or bootie to reduce chance of dislodging overnight
7. Secure cable with tape to ankle or lower leg.
8. The sensor can be discontinued from the cable for short periods during the night if baby cares are required

Discontinuation & download in the morning
1. After 12 hours, please remove the sensor from baby’s foot and turn the machine off.
2. DO NOT REMOVE THE MACHINE FROM THE POWER SOCKET. If for any reason the oximeter machine needs to be moved out of the room, please place in a secure area and plug into wall.
3. The Research Team will be responsible for removing and downloading data in the morning
Once a baby is consented and randomised, the baby will be allocated to a study group and a treatment group letter. The research team will collect the allocated medication, maintain stock control and arrange for the medication to be charted and dispensed.

A dose adjustment is made at two weeks of age provided that baby is back at birth weight. If baby is not yet at birth weight, maintain current dosing and review weight and dosage again in one week.

**Study Schedule**

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<th></th>
<th>Co-ordinator: Lisa Mravicich</th>
<th>Co-ordinator: Florella Keen</th>
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<tr>
<td></td>
<td>Baseline</td>
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<td>Loading dose</td>
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<td>Dose adjustment for weight</td>
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<tr>
<td>Neonatal salivary caffeine concentration</td>
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<tr>
<td>Maternal salivary caffeine concentration</td>
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<td>Edinburgh Postnatal Depression Scale</td>
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**Participant Withdrawal**

- Research Team to end the iPIMS alert (do not delete)
- Research Team to process a Soprano ‘Withdrawal from Study’ letter to GP
- Remove all study drug medication from parents & document stop date on medication chart
- Document in MCIS & clinical notes that participant has been withdrawn
- eCRF’s to be shown as incomplete