**BACKGROUND**

Late preterm infants (34\textsuperscript{th} to 36\textsuperscript{th} weeks' gestational age) are the largest group of preterm infants, constituting 6\% of all births or 3,700 births annually in New Zealand.\textsuperscript{1} These infants have a 3-4 fold increased risk of cerebral palsy and 30-50\% increased risk of neurodevelopmental impairment and poor educational achievement compared to infants born at term.\textsuperscript{2,3} 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,\textsuperscript{4} but also improves long-term neurodevelopmental outcomes, especially motor function and visual perception.\textsuperscript{5}

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,\textsuperscript{6} but there are no data to show if caffeine improves long-term neurodevelopmental outcomes, especially motor function and visual perception.\textsuperscript{7}

The most effective dose of caffeine at this gestational age is also uncertain. Very preterm infants have limited ability to metabolise caffeine, but this increases with greater gestational age.\textsuperscript{9} 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.

Before initiating wider studies to investigate effects on neurodevelopment, we must first determine the safest and most effective dose of caffeine in late preterm infants. This is the aim of the Latte Dosage Trial.

**PURPOSE OF THE TRIAL**

To determine the most effective and best tolerated dose of caffeine to reduce intermittent hypoxia in late preterm infants.

**ENTRY CRITERIA**

**Inclusion Criteria:**
1. Born between 34\textsuperscript{th} to 36\textsuperscript{th} weeks' gestation and <72 hours of age
2. No contraindication to caffeine
3. Prospective, written, informed consent obtained

**Exclusion Criteria:**
1. Congenital abnormality likely to affect respiration, growth or development
2. Previous caffeine treatment
3. Renal or hepatic impairment
4. Tachyarrhythmia
5. Seizures or hypoxic ischaemic encephalopathy
6. Residing outside of the Auckland or Counties Manukau DHB region

**STUDY GROUPS**

Eligible infants will be randomly allocated within 72 hours of birth to either caffeine citrate 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg or placebo, stratified by study site and gestational age at birth (Figure) and continued until term equivalent age (40 weeks' gestation). Twins will be randomised to the same treatment group.

Infants will be allocated a letter (A to E) corresponding 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 to maintain blinding (1 ml/kg, once daily). A loading dose of 2 ml/kg will be given on the first day of trial. All study medicine will be given in the morning.

**OUTCOMES**

**Primary:**
Frequency of intermittent hypoxaemia (mean events/hour, defined as oxygen saturation concentration ≥10\% below baseline for any duration) on overnight oximetry, two weeks after randomisation.

**Secondary:**
- Frequency of intermittent hypoxaemia at term equivalent age
- Mean overnight oxygen saturation
- Weight gain from birth to term equivalent age
- Duration of tube feeding
- Maternal and baby salivary caffeine concentration
- Maternal daily caffeine intake
- Edinburgh postnatal depression score
- Tachycardia (percentage of time HR >180 beats/min)
- Feed intolerance
- Sleeping and arousal
Other adverse events

**SAMPLE SIZE**
A sample size of 120 (24 per group) will have 90% power to detect a 50% reduction in the mean rate of intermittent hypoxia from 6.9 episodes per hour to 3.5 episodes per hour, allowing for 10% drop out rate.

**CO-INTERVENTION**
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 unblinding the infant (caffeine yes / no) with the Site Principal Investigator.

**REFERENCES**

**Investigators:**
Dr Jane Alsweiler (Principal Investigator), Dr David McNamara (Paediatric Respiratory Physician), Dr Chris McKinlay (Counties Manukau Site Principal Investigator), Elizabeth Oliphant (Paediatric Pharmacist).

**Study Team:**
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