❖ BACKGROUND

Late preterm infants (34^{+0} to 36^{+6} weeks' gestational age) are the largest group of preterm infants, constituting 6% of all births or 3,700 births annually in New Zealand.[1] Currently, systemic privilege and advantage in outcomes occurs for European women and their babies. Equity is a priority for all aspects of health and wellbeing, including late preterm babies, 20% of whom are Māori. Late preterm 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 term infants.[2-4] 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 neurodevelopmental outcomes, especially motor function and visual perception. [5]

While apnoea of prematurity is less common in late preterm infants, infants born late preterm are at increased risk of intermittent hypoxaemia. We have recently completed the Latte Dosage Trial, which randomized 132 late preterm babies to one of four daily doses of caffeine citrate (5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg) or placebo with a primary outcome of intermittent hypoxaemia at 2 weeks post randomisation.[6] Caffeine citrate at 10 mg/kg and 20 mg/kg day reduced intermittent hypoxaemia and increased the mean SpO_2 (Figure). Currently, there are no data to show if caffeine improves long-term neurodevelopmental outcomes in infants born late preterm.

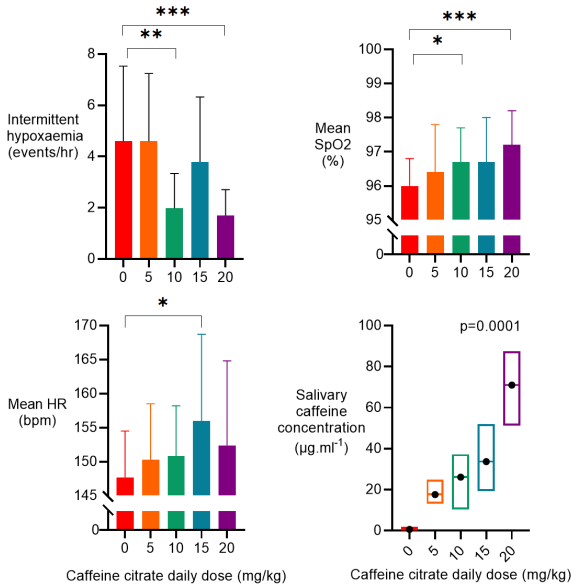

Figure. The effect of different daily doses of caffeine citrate on intermittent hypoxaemia (geometric mean (95%CI), mean SpO2, heart rate, and salivary caffeine concentration (median (IQR), in late preterm babies at 2 weeks of age. * p<0.05, ** p<0.01, ***p<0.005

❖ PURPOSE OF THE TRIAL

To determine if prophylactic caffeine citrate treatment, given to babies born late preterm (34+0 to 36+6) from birth to term equivalent age improves neurodevelopmental outcome at 2.5 years' corrected age.

❖ ENTRY CRITERIA

Inclusion Criteria:

1. Born between 34^{+0} to 36^{+6} 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. Maternal age less than 16 years
7. Multiple births of triplets or higher

❖ PARTICIPANTS

Potentially eligible late preterm babies will be identified on antenatal wards, neonatal units, and postnatal wards. We will intentionally place an emphasis on recruiting Māori whānau in this study to assist Mana Whakamārama (equal explanatory power) to occur and aim for 50% of participants to be Māori.

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

❖ OUTCOMES

Primary:

Bayley Scale of Infant Development 4th Edition (BSID IV) cognitive score at 2.5 years' corrected age.

Secondary outcomes include:

Neonatal

- anthropometry
- length of stay
- study drug tolerance
- breastfeeding

Early childhood (2.5 years corrected age)

- cognitive, motor or language impairment (BSID IV)
- developmental delay
- pre-school wheeze
- death
- anthropometry
- health related quality of life
- healthcare utilisation

❖ SAMPLE SIZE

To detect a difference between caffeine and placebo groups of at least 5 points with 90% power (two-sided α=0.05) requires 191 babies in each arm (total 382). Allowing for a conservative 20% drop-out rate (withdrawal and loss to follow-up), we will recruit a total of 478 babies (239 in each arm).

❖ 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 un-blinding the infant (caffeine yes / no) with the Site Principal Investigator.

Investigators:

Assoc Prof Jane Alsweiler (Chair, Neonatologist)
Assoc Prof Chris McKinlay (Neonatologist)
Dr David McNamara (Paediatric Respiratory Specialist)
Dr Liza Edmonds ((Ngāpuhi, Ngāti Whātua, Neonatologist)
Ms Jenny Rogers (Ngāi Tahu, Kāi Tahu, Kaiarahi)
Dr Braden Te Ao (Waikato, Tainui, Health Economist)
Dr Alana Cavadino (Statistician)
Ms Elizabeth Oliphant (Paediatric Pharmacist)

Funding:

This trial has been funded by a project grant by the Health Research Council of New Zealand. Funding will be provided to each site for Research nurse time. Study drug will be formulated and delivered by Biomed. Developmental assessments at 2.5 years can either be organised and performed by a central University of Auckland follow-up team who will travel to the sites, or payment can be made for sites to do their own follow-up.

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The LATTE TRIAL

Caffeine prophylaxis to improve neurodevelopment in babies born late preterm: a randomised controlled trial

LATTE

HEALTH PROFESSIONAL INFORMATION SHEET

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