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# Caffeine to prevent intermittent hypoxaemia in late preterm infants: randomised controlled dosage trial

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## ABSTRACT

**Objective** To establish the most effective and best tolerated dose of caffeine citrate for the prevention of intermittent hypoxaemia (IH) in late preterm infants.

**Design** Phase IIB, double-blind, five-arm, parallel, randomised controlled trial.

**Setting** Neonatal units and postnatal wards of two tertiary maternity hospitals in New Zealand.

**Participants** Late preterm infants born at $34^{+0}$–$36^{+6}$ weeks' gestation, recruited within 72 hours of birth.

**Intervention** Infants were randomly assigned to receive a loading dose (10, 20, 30 or 40 mg/kg) followed by 5, 10, 15 or 20 mg/kg/day equivolume enteral caffeine citrate or placebo daily until term corrected age.

**Primary outcome** IH (events/hour with oxygen saturation concentration ≥10% below baseline for ≤2 min), 2 weeks postrandomisation.

**Results** 132 infants with mean (SD) birth weight 2561 (481) g and gestational age 35.7 (0.8) weeks were randomised (24–28 per group). Caffeine reduced the rate of IH at 2 weeks postrandomisation (geometric mean (GM): 4.6, 4.6, 2.0, 3.8 and 1.7 events/hour for placebo, 5, 10, 15 and 20 mg/kg/day, respectively), with differences statistically significant for 10 mg/kg/day (GM ratio (95% CI] 0.39 (0.20 to 0.76]; p=0.006) and 20 mg/kg/day (GM ratio (95% CI] 0.33 (0.17 to 0.68]; p=0.003) compared with placebo. The 20 mg/kg/day dose increased mean (SD) pulse oximetry oxygen saturation ($SpO_2$) (97.2 (1.0) vs placebo 96.0 (0.8); p<0.001), and reduced median (IQR) percentage of time $SpO_2$ <90% (0.5 (0.2–0.8) vs 1.1 (0.6–2.4); p<0.001) at 2 weeks, without significant adverse effects on growth velocity or sleeping.

**Conclusion** Caffeine reduces IH in late preterm infants at 2 weeks of age, with 20 mg/kg/day being the most effective dose.

**Trial registration number** ACTRN12618001745235.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hypoxaemia is associated with negative effects on cognition and neurodevelopmental outcomes in preterm infants and episodes of intermittent hypoxaemia are more common in late preterm infants than their term-born peers.

⇒ Caffeine reduces episodes of apnoea of prematurity and intermittent hypoxaemia and improves neurodevelopmental outcomes in very preterm infants.

### WHAT THIS STUDY ADDS

⇒ Doses of 10 or 20 mg/kg/day of caffeine citrate are effective at reducing intermittent hypoxaemia in late preterm infants, without adverse effects on gastrointestinal reflux or sleep, but with an increase in tachycardia.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If caffeine is proven to improve neurodevelopmental outcomes in late preterm infants, widespread use could provide long-term benefits for brain development in this important patient group.

⇒ Establishing an effective dose that is associated with minimal side effects is a necessary step towards this goal and allows the development of a larger and long-term trial of effectiveness.

## INTRODUCTION

Late preterm infants ($34^{+0}$–$36^{+6}$ weeks' gestation) comprise the majority of preterm births,[1 2] and are physiologically and metabolically immature,[3] with a higher risk of morbidity and mortality in the neonatal period than term infants.[4] Late preterm infants are more likely to be diagnosed with cerebral palsy,[5 6] developmental delay[7–9] and cognitive impairment[9–13] compared with term infants. Late preterm infants also experience frequent episodes of intermittent hypoxaemia (IH)[14]; transient repetitive decreases in oxygen saturation not associated with apnoea but potentially causing similar organ hypoxia. The frequency of these episodes peaks at 2 weeks' postnatal age, before reducing to near-birth levels at term corrected age.[14] During the neonatal period, even small changes in pulse oximetry oxygen saturations ($SpO_2$) significantly affect survival and neurodevelopment of very preterm infants[15–17] and transient intermittent hypoxaemic events are associated with poor neurodevelopmental outcomes in extremely preterm infants.[18]

Caffeine is effective in the prevention and treatment of apnoea of prematurity and IH, and reduces the incidence of chronic lung disease, cerebral palsy and cognitive delay in very preterm infants.[19–21] Due to hepatic immaturity, caffeine elimination is slow in extremely preterm infants.[22] With increasing gestational age the elimination of caffeine increases,[22 23] requiring larger doses to maintain a therapeutic effect.[24] In very preterm infants caffeine is usually well tolerated, but can reduce neonatal weight gain and occasionally infants on caffeine develop tachycardia and feed intolerance.[20 25] The most effective dose of caffeine to treat IH in late preterm infants remains unknown.

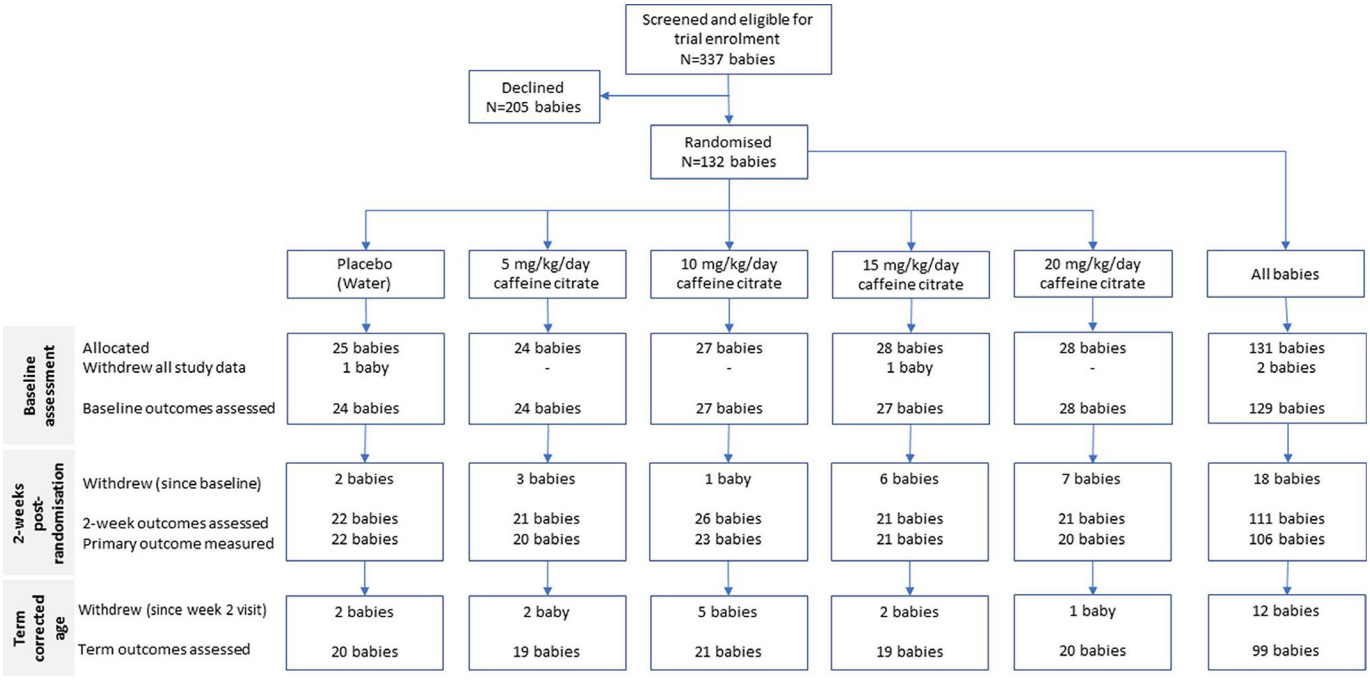


**Figure 1** Flow diagram of trial participants.

## Aim

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

## METHODS

The study protocol of the Latte Dosage Trial has been reported previously.[26] Briefly, late preterm infants delivered at two maternity hospitals in Auckland, New Zealand were eligible if born between $34^{+0}$ and $36^{+6}$ weeks' gestation, without relevant exclusions (major congenital abnormality, minor congenital abnormality likely to affect respiration, growth or development, previous caffeine treatment or contraindications to caffeine). Following parental consent, participating infants were randomised by a member of the trial team to one of five parallel groups (5, 10, 15 or 20 mg/kg/day of caffeine citrate or placebo) within 72 hours of birth using an internet randomisation service with varying block sizes and 1:1:1:1:1 allocation stratified by study site and gestational age at birth (34, 35 or 36 weeks). Twins were allocated to the same group. Participating infants received an enteral loading dose of study drug (10, 20, 30 or 40 mg/kg of caffeine citrate or placebo (water)) followed by a daily dose each morning (5, 10, 15 or 20 mg/kg of caffeine citrate or placebo) until term equivalent age (TEA; 40 weeks' postmenstrual age), with the dose recalculated weekly for weight gain. Trial medication was prepared at various strengths, so each infant received the same volume (2 mL/kg loading dose; 1 mL/kg/day thereafter) of identical-appearing trial medication. Parents, clinical staff and those assessing outcomes were all blinded to treatment group, and all other care decisions, including discharge, were made by the clinical team. Postdischarge, babies were cared for at home by parents, who continued to give the trial medication until the final visit at TEA.

Participating infants, whether in hospital or at home, underwent overnight oximetry using a motion-resistant oximeter (Masimo Rad-8, Masimo, Irvine, California, USA) prior to administration of the loading dose, at 2 weeks postrandomisation and TEA. Oximetry recordings had a 2 s averaging time and were edited by a single investigator using Profox software (Profox Associates, Coral Springs, Florida, USA) to automatically remove low confidence and aberrant data, followed by a final manual review.[27] A minimum of 6 hours of edited data was required. At the same timepoints, data were collected on maternal caffeine intake[28] and infant feeding,[29] sleeping[30 31] and anthropometry. Saliva samples were collected from mothers (three samples across an 8-hour daytime period) and infants (prior to the study drug) at the 2-week timepoint and analysed to determine caffeine concentrations.[32]

The primary outcome was the rate of IH (events/hour, $SpO_2$ fall ≥10% below baseline for >2 s and <2 min) on overnight oximetry, 2 weeks postrandomisation. Prespecified secondary outcomes are available in the protocol,[26] and included neonatal growth, tachycardia and salivary caffeine concentrations.

Based on our previous study,[14] we estimated a mean (SD) rate of 6.9 (3.4) IH episodes per hour at 2 weeks' postrandomisation. To detect a 50% reduction (3.5 episodes per hour) in any group versus placebo with 90% power, allowing for a 10% drop out and clustering of multiples (intraclass correlation coefficient 0.05) would require 24 infants in each group (total 120 infants), with two-sided $\alpha=0.05$. The trial was not powered to conduct comparisons between caffeine doses.

Statistical analysis was performed using Stata (V.16). Caffeine groups were compared with the placebo group for outcomes using generalised linear mixed models,[33] with adjustment for gestational age at birth, site and non-independence of multiples. Analysis was intention-to-treat, with separate models for each timepoint. Distributions of outcome variables and model residuals were visually assessed for deviations from normality, where data were highly skewed, a log transformation was used to improve model fit. Treatment effects are expressed as mean difference, geometric mean ratio (RGM) or OR, with 95% CIs.

Prespecified secondary analyses for the primary outcome included a comparison of infants allocated to placebo with those allocated to any dose of caffeine citrate (ie, all caffeine groups combined), a per-protocol analysis of infants who received the

**Table 1** Baseline characteristics of 121 mothers and 129 infants participating in the Latte Dosage Trial

| | Placebo | Caffeine citrate 5 mg/kg/day | Caffeine citrate 10 mg/kg/day | Caffeine citrate 15 mg/kg/day | Caffeine citrate 20 mg/kg/day | Any dose of caffeine |
|---|---|---|---|---|---|---|
| Number of mothers (% of total) | 24 (19.8) | 23 (19.0) | 24 (19.8) | 25 (20.7) | 25 (20.7) | 97 (80.2) |
| Age (years) | 31.1 (6.0) | 31.6 (5.3) | 30.6 (5.5) | 32.1 (5.8) | 31.3 (6.3) | 31.4 (5.7) |
| Primiparous | 9 (37.5) | 11 (47.8) | 16 (66.7) | 15 (60.0) | 13 (52.0) | 55 (56.7) |
| Body mass index (kg/m$^2$) | 26.1 (23.5, 30.7) | 27.9 (24.2, 31.5) | 26.3 (23.3, 30.6) | 24.9 (21.9, 28.4) | 28.6 (23.4, 32.5) | 26.5 (23.2, 30.1) |
| Multiple pregnancy | 0 (0.0) | 1 (4.3) | 3 (12.5) | 2 (8.0) | 2 (8.0) | 8 (8.2) |
| Antenatal events | | | | | | |
| Maternal diabetes | 5 (20.8) | 3 (13.0) | 9 (37.5) | 2 (8.0) | 7 (28.0) | 21 (21.6) |
| Preterm prelabour rupture of membranes | 12 (50.0) | 13 (56.5) | 8 (33.3) | 15 (60.0) | 8 (32.0) | 44 (45.4) |
| Preterm labour | 20 (83.3) | 18 (78.3) | 13 (54.2) | 19 (76.0) | 17 (68.0) | 67 (69.1) |
| Hypertension in pregnancy | 3 (12.5) | 1 (4.3) | 4 (16.7) | 2 (8.0) | 5 (20.0) | 12 (12.4) |
| Antepartum haemorrhage | 1 (4.2) | 6 (26.1) | 1 (4.2) | 5 (20.0) | 2 (8.0) | 14 (14.4) |
| Suspected fetal growth restriction | 3 (12.5) | 3 (13.0) | 6 (25.0) | 4 (16.0) | 6 (24.0) | 19 (19.6) |
| Antenatal glucocorticosteroids | 5 (20.8) | 4 (17.4)* | 8 (33.3) | 8 (32.0)* | 4 (16.0) | 24 (24.7) |
| Number of infants (% of total) | 24 (18.6) | 24 (18.6) | 27 (20.9) | 27 (20.9) | 27 (20.9) | 105 (81.5) |
| Gestational age (weeks) | | | | | | |
| 34 | 6 (25.0) | 5 (20.8) | 6 (22.2) | 5 (18.5) | 6 (22.2) | 22 (21.0) |
| 35 | 7 (29.2) | 8 (33.3) | 9 (33.3) | 10 (37.0) | 9 (33.3) | 36 (34.3) |
| 36 | 11 (45.8) | 11 (45.8) | 12 (44.4) | 12 (44.4) | 12 (44.4) | 47 (44.8) |
| Sex (male) | 14 (58.3) | 17 (70.8) | 12 (44.4) | 18 (66.7) | 16 (59.3) | 63 (60.0) |
| Singleton† | 24 (100.0) | 22 (91.7) | 21 (77.8) | 23 (85.2) | 23 (85.2) | 89 (84.8) |
| Ethnicity (prioritised) | | | | | | |
| Māori | 2 (8.3) | 6 (25.0) | 1 (3.7) | 2 (7.4) | 7 (25.9) | 16 (15.2) |
| Pacific Islander | 7 (29.2) | 5 (20.8) | 2 (7.4) | 5 (18.5) | 5 (18.5) | 17 (16.2) |
| Asian | 7 (29.2) | 5 (20.8) | 13 (48.1) | 11 (40.7) | 7 (25.9) | 36 (34.3) |
| Other | 1 (4.2) | 1 (4.2) | 1 (3.7) | 1 (3.7) | 1 (3.7) | 4 (3.8) |
| NZ European | 7 (29.2) | 7 (29.2) | 10 (37.0) | 8 (29.6) | 7 (25.9) | 32 (30.5) |
| Birth weight (g) | 2566.5 (272.2) | 2674.6 (480.6) | 2523.9 (603.7) | 2641.9 (432.5) | 2393.3 (515.1) | 2555.1 (517.3) |
| Z-score‡ | −0.0 (0.7) | 0.2 (1.1) | −0.1 (1.3) | 0.1 (1.0) | −0.5 (1.1) | −0.1 (1.1) |
| Length (cm) | 47.8 (2.0) | 48.9 (2.5) | 47.2 (3.4) | 47.8 (2.1) | 46.8 (3.2) | 47.6 (2.9) |
| Z-score‡ | 0.5 (0.6) | 1.0 (1.0) | 0.3 (1.3) | 0.5 (0.9) | 0.1 (1.1) | 0.5 (1.1) |
| Head circumference (cm) | 32.4 (1.2) | 33.8 (1.5) | 32.5 (1.8) | 33.1 (1.5) | 32.3 (1.7) | 32.9 (1.7) |
| Z-score‡ | 0.2 (0.8) | 1.0 (1.0) | 0.2 (1.2) | 0.6 (1.1) | −0.0 (1.0) | 0.4 (1.1) |
| Caesarean delivery | 8 (33.3) | 10 (41.7) | 15 (55.6) | 12 (44.4) | 10 (37.0) | 47 (44.8) |
| Apgar score (5 min) | 9.0 (9.0, 10.0) | 9.0 (8.0, 10.0) | 10.0 (9.0, 10.0) | 9.0 (9.0, 10.0) | 9.0 (9.0, 10.0) | 9.0 (9.0, 10.0) |
| Admitted to neonatal intensive care | 12 (50.0) | 12 (50.0) | 13 (48.1) | 13 (48.1) | 17 (63.0) | 55 (52.4) |
| Positive pressure respiratory support prior to enrolment | 8 (33.3) | 7 (29.2) | 6 (22.2) | 9 (33.3) | 6 (22.2) | 28 (26.7) |
| Oxygen prior to enrolment | 2 (8.3) | 3 (12.5) | 4 (14.8) | 4 (14.8) | 3 (11.1) | 14 (13.3) |

Data are mean (SD), median (IQR) or n (%).
*N=1 with missing data in this group.
†In some cases, only one infant was eligible for the trial or a twin pregnancy resulted in a single live birth.
‡Z-scores were calculated from the revised Fenton growth charts for preterm infants.[42]

correct intervention and were compliant with the protocol[26] (80% of study drug administered at 2 weeks), a sensitivity analysis excluding multiples and exploratory analyses adjusting separately for baseline oximetry, and maternal caffeine intake and salivary caffeine concentrations at 2 weeks. Wilcoxon rank-sum tests were used to compare maternal caffeine intake and salivary concentrations, due to highly skewed distributions. A two-tailed $p<0.05$ was considered statistically significant. Kenward-Roger correction was applied to mixed models to maintain nominal error rate. Additional adjustment for testing of multiple secondary outcomes was not performed and these results are interpreted cautiously, cognisant of the risk of type I error.

The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12618001745235).

## RESULTS

Between February 2019 and December 2020, 131 infants were randomly allocated to placebo or one of four caffeine citrate groups, with primary outcome data available for 107 infants (figure 1). Baseline characteristics were similar across groups (table 1). The mean (SD) duration of overnight oximetry recordings after editing was 10.6 (1.9) hours.

The rate of IH at 2 weeks postrandomisation was significantly reduced among infants allocated to caffeine citrate 10 or 20 mg/kg/day compared with placebo (RGM (95% CI] 0.39 (0.20 to 0.76] and 0.33 (0.17 to 0.68], respectively), but not for the 5 or 15 mg/kg/day groups (table 2). The rate of IH was significantly reduced for infants allocated to any dose of caffeine

**Table 2** Primary outcome and cardiorespiratory secondary outcomes

| | Placebo N=24* | Caffeine citrate 5mg/kg/day N=24* | | Caffeine citrate 10mg/kg/day N=27* | | Caffeine citrate 15 mg/kg/day N=27* | | Caffeine citrate 20 mg/kg/day N=27* | | Any dose of caffeine N=105* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Summary data | Summary data | RGM or mean difference (95% CI); p value† | Summary data | RGM or mean difference (95% CI); p value† | Summary data | RGM or mean difference (95% CI); p value† | Summary data | RGM or mean difference (95% CI); p value† | Summary data | RGM or mean difference (95% CI); p value† |
| Primary outcome | | | | | | | | | | | |
| Rate of intermittent hypoxaemia at 2 weeks; median (IQR) (geometric mean) | 4.0 (1.8, 9.8) (4.6) | 5.9 (2.8, 7.6) (4.6) | 0.97 (0.49 to 1.95); 0.94 | 2.5 (0.6, 5.7) (2.0) | 0.39 (0.20 to 0.76); 0.006 | 3.3 (2.1, 8.8) (3.8) | 0.79 (0.40 to 1.56); 0.49 | 1.8 (0.9, 4.2) (1.7) | 0.33 (0.17 to 0.68); 0.003 | 3.0 (1.3, 6.1) (2.7) | 0.56 (0.32 to 0.98); 0.043 |
| Secondary outcomes | | | | | | | | | | | |
| Rate of intermittent hypoxaemia; median (IQR) (geometric mean) | | | | | | | | | | | |
| Baseline | 0.9 (0.6, 1.4) | 2.0 (0.9, 3.3) | | 1.1 (0.7, 2.0) | | 1.9 (1.1, 2.6) | | 1.5 (0.8, 4.4) | | 1.5 (0.9, 2.8) | |
| Term | 3.0 (1.9, 6.2) (3.3) | 4.0 (1.9, 6.9) (3.4) | 1.02 (0.50 to 2.07); 0.96 | 2.5 (1.0, 6.1) (2.4) | 0.65 (0.33 to 1.32); 0.23 | 3.3 (1.5, 8.2) (3.1) | 0.82 (0.40 to 1.69); 0.59 | 2.2 (1.0, 4.7) (1.9) | 0.54 (0.26 to 1.11); 0.09 | 2.9 (1.3, 6.7) (2.7) | 0.75 (0.43 to 1.30); 0.30 |
| Mean $SpO_2$; mean (SD) | | | | | | | | | | | |
| Baseline | 96.4 (1.3) | 96.4 (1.5) | | 95.6 (1.8) | | 96.6 (1.4) | | 95.5 (2.0) | | 96.0 (1.7) | |
| Two weeks | 96.0 (0.8) | 96.4 (1.4) | 0.39 (−0.28 to 1.07); 0.25 | 96.7 (1.0) | 0.68 (0.04 to 1.33); 0.039 | 96.7 (1.3) | 0.66 (−0.01 to 1.33); 0.06 | 97.2 (1.0) | 1.31 (0.62 to 2.00); <0.001 | 96.8 (1.2) | 0.74 (0.21 to 1.28); 0.007 |
| Term | 97.3 (1.0) | 97.5 (0.9) | 0.13 (−0.61 to 0.87); 0.72 | 97.2 (0.8) | 0.09 (−0.64 to 0.82); 0.81 | 97.2 (1.2) | 0.05 (−0.70 to 0.81); 0.89 | 97.4 (1.7) | 0.30 (−0.46 to 1.06); 0.44 | 97.3 (1.2) | 0.14 (−0.43 to 0.71); 0.62 |
| Percentage of time $SpO_2$ <90%; median (IQR) | | | | | | | | | | | |
| Baseline | 1.1 (0.3, 1.6) | 1.2 (0.5, 2.4) | | 1.2 (0.3, 1.9) | | 1.0 (0.6, 1.4) | | 1.5 (0.5, 3.1) | | 1.2 (0.5, 2.3) | |
| Two weeks | 1.1 (0.6, 2.4) (1.3) | 1.0 (0.7, 2.0) (1.1) | 0.83 (0.43 to 1.60); 0.58 | 0.9 (0.3, 1.6) (0.6) | 0.40 (0.21 to 0.75); 0.005 | 0.7 (0.4, 1.6) (0.8) | 0.63 (0.33 to 1.22); 0.17 | 0.5 (0.2, 0.8) (0.4) | 0.29 (0.14 to 0.56); <0.001 | 0.7 (0.3, 1.6) (0.7) | 0.50 (0.29 to 0.85); 0.011 |
| Term | 0.6 (0.3, 1.1) (0.6) | 0.5 (0.3, 1.3) (0.6) | 0.89 (0.43 to 1.84); 0.76 | 0.4 (0.3, 1.1) (0.5) | 0.75 (0.37 to 1.53); 0.43 | 0.6 (0.4, 1.3) (0.6) | 0.84 (0.40 to 1.77); 0.65 | 0.3 (0.2, 1.7) (0.4) | 0.59 (0.28 to 1.22); 0.15 | 0.5 (0.2, 1.3) (0.5) | 0.76 (0.43 to 1.34); 0.34 |
| Mean heart rate; mean (SD) | | | | | | | | | | | |
| Baseline | 130.1 (9.0) | 130.0 (6.8) | | 134.0 (10.2) | | 132.1 (10.4) | | 130.8 (9.3) | | 131.7 (9.3) | |
| Two weeks | 147.7 (6.8) | 150.3 (8.2) | 3.07 (−5.32 to 4.63); 0.89 | 150.8 (7.4) | 3.43 (−2.22 to 9.08); 0.23 | 156.0 (12.7) | 8.44 (2.59 to 14.30); 0.005 | 152.4 (12.4) | 3.75 (−2.28 to 9.79); 0.22 | 152.3 (10.4) | 4.63 (0.04 to 9.21); 0.048 |
| Term | 150.8 (8.6) | 150.3 (6.9) | −0.35 (−5.25 to 4.55); 0.89 | 152.3 (5.7) | 1.26 (−3.66 to 6.19); 0.61 | 155.5 (8.9) | 4.37 (−0.69 to 9.42); 0.09 | 151.1 (8.5) | 0.07 (−5.05 to 5.19); 0.98 | 152.3 (7.6) | 1.28 (−2.62 to 5.17); 0.52 |
| Percentage of time HR >180; median (IQR) | | | | | | | | | | | |
| Baseline | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.4) | | 0.1 (0.0, 0.3) | | 0.0 (0.0, 0.3) | | 0.0 (0.0, 0.2) | | 0.0 (0.0, 0.3) | |
| Two weeks | 0.9 (0.2, 5.2) (0.9) | 3.1 (2.0, 8.9) (3.8) | 4.34 (1.87 to 10.10); 0.001 | 4.3 (2.4, 9.0) (3.8) | 4.03 (1.79 to 9.08); 0.001 | 7.0 (4.0, 10.1) (5.5) | 5.94 (2.56 to 13.77); <0.001 | 7.4 (4.4, 13.9) (6.1) | 5.71 (2.40 to 13.57); <0.001 | 6.0 (2.9, 10.0) (4.7) | 4.87 (2.55 to 9.29); <0.001 |
| Term | 2.0 (0.4, 5.6) (1.6) | 4.7 (3.0, 8.0) (3.9) | 2.50 (1.07 to 5.86); 0.035 | 5.5 (2.4, 9.4) (4.6) | 2.86 (1.23 to 6.63); 0.015 | 5.6 (2.7, 9.9) (3.6) | 2.22 (0.93 to 5.27); 0.07 | 6.7 (4.4, 10.7) (5.2) | 3.19 (1.33 to 7.65); 0.010 | 5.7 (2.7, 9.0) (4.3) | 2.66 (1.39 to 5.11); 0.004 |
| Compliant‡ with administration schedule at 2 weeks | 21 (87.5%) | 18 (78.5%) | 0.33 (0.06 to 1.91); 0.22 | 23 (85.2%) | 0.54 (0.09 to 3.41); 0.51 | 19 (70.4%) | 0.20 (0.04 to 1.14); 0.07 | 18 (66.7%) | 0.21 (0.04 to 1.24); 0.09 | 78 (73.6%) | 0.28 (0.06 to 1.33); 0.11 |
| Study drug stopped due to presumed side effects§ | 2 (9.1%) | 4 (16.7%) | 2.07 (0.32 to 13.18); 0.44 | 5 (19.2%) | 2.49 (0.37 to 16.75); 0.35 | 7 (28.0%) | 4.21 (0.68 to 26.13); 0.12 | 6 (22.2%) | 2.96 (0.49 to 17.75); 0.23 | 22 (21.6%) | 2.88 (0.58 to 14.31) 0.20 |

*Number of infants with oximetry traces of usable quality (% of total remaining in study in that group) at baseline, 2 weeks and term, respectively, are: 20 (83.3%), 22 (100%), 20 (100%) in placebo group; 23 (95.8%), 20 (100%), 18 (94.7%) in 5 mg/kg/day group; 26 (96.3%), 24 (96.0%), 20 (95.2%) in 10 mg/kg/day group; 27 (100%), 21 (100%), 18 (94.7%) in 15 mg/kg/day group and 25 (89.3%), 20 (100%), 17 (85.0%) in 20 mg/kg/day group.
†Where the mean (SD) is presented the exposure effect is a mean difference; where median (IQR) and geometric mean are presented the exposure effect is the RGM. For all comparisons the reference category is the placebo group.
‡Compliant is defined as <20% of the expected study drug volume (as calculated for that child based on birth weight) remaining in the bottle when measured by the research team at the 2-week visit (ie, >80% of the study drug has been removed from the bottle). Information on compliance at 2 weeks is missing for n=4 (1 in each group except 10 mg/kg).
§Further breakdown of reasons for withdrawals is provided in the online supplemental tables.
RGM, geometric mean ratio.

**Table 3** Secondary outcomes

| | Placebo N=24* | Caffeine citrate 5 mg/kg/day N=24 | | Caffeine citrate 10 mg/kg/day N=27 | | Caffeine citrate 15 mg/kg/day N=27 | | Caffeine citrate 20 mg/kg/day N=27 | | Any dose of caffeine N=105 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Summary data | Summary data | Mean difference (95% CI), p value vs placebo | Summary data | Mean difference (95% CI), p value vs placebo | Summary data | Mean difference (95% CI), p value vs placebo | Summary data | Mean difference (95% CI), p value vs placebo | Summary data | Mean difference (95% CI), p value vs placebo |
| Weight growth velocity (birth to term equivalent) (g/kg/day)*, †; mean (SD) | 8.8 (3.1) | 8.4 (3.4) | −0.45 (−2.55 to 1.65); 0.67 | 7.5 (3.4) | −1.51 (−3.59 to 0.56); 0.15 | 9.1 (3.4) | 0.02 (−2.10 to 2.15); 0.98 | 9.1 (3.5) | −0.32 (−2.51 to 1.88); 0.78 | 8.5 (3.4) | −0.62 (−2.27 to 1.04); 0.46 |
| Length growth velocity (birth to term equivalent) (cm/week)*· †; mean (SD) | 0.7 (0.6) | 0.7 (0.4) | −0.08 (−0.39 to 0.23); 0.61 | 0.7 (0.6) | 0.02 (−0.28 to 0.33); 0.89 | 1.0 (0.4) | 0.20 (−0.11 to 0.52); 0.20 | 0.6 (0.4) | −0.08 (−0.41 to 0.25); 0.62 | 0.8 (0.5) | 0.02 (−0.23 to 0.26); 0.89 |
| Head circumference growth velocity (birth to term equivalent) (cm/week)*· †; mean (SD) | 0.6 (0.3) | 0.4 (0.2) | −0.23 (−0.40 to −0.07); 0.006 | 0.5 (0.3) | −0.12 (−0.28 to 0.04); 0.15 | 0.5 (0.2) | −0.16 (−0.33 to 0.00); 0.05 | 0.5 (0.2) | −0.16 (−0.34 to 0.01); 0.07 | 0.5 (0.2) | −0.17 (−0.30 to −0.04); 0.010 |
| Failure to regain birth weight by 2 weeks postnatal age; N (%)‡ | 2 (8.3%) | 2 (8.3%) | 1.03 (0.13 to 8.21); 0.98 | 4 (14.8%) | 1.91 (0.28, 13.29); 0.51 | 7 (25.9%) | 4.33 (0.72 to 26.16); 0.11 | 6 (21.4%) | 3.50 (0.55 to 22.30); 0.18 | 19 (17.9%) | 2.58 (0.51 to 13.11); 0.25 |
| Sleep score; mean (SD)§,¶ | | | | | | | | | | | |
| Two weeks | 4.2 (0.6) | 4.3 (0.3) | 0.11 (−0.17 to 0.38); 0.45 | 4.3 (0.5) | 0.02 (−0.25 to 0.29); 0.87 | 4.2 (0.3) | 0.01 (−0.27 to 0.29); 0.94 | 4.1 (0.5) | −0.09 (−0.38 to 0.20); 0.53 | 4.2 (0.4) | 0.02 (−0.20 to 0.23); 0.87 |
| Term | 4.4 (0.5) | 4.4 (0.3) | 0.05 (−0.21 to 0.31); 0.70 | 4.5 (0.4) | 0.16 (−0.09 to 0.42); 0.21 | 4.3 (0.4) | −0.03 (−0.30 to 0.23); 0.80 | 4.2 (0.4) | −0.18 (−0.44 to 0.09); 0.19 | 4.4 (0.4) | 0.01 (−0.20 to 0.22); 0.94 |
| Gastro-oesophageal symptoms; I-GERQ-R mean (SD)§ | | | | | | | | | | | |
| Two weeks | 29.7 (4.3) | 27.6 (4.2) | −2.35 (−5.56 to 0.85); 0.15 | 25.3 (6.1) | −3.80 (−6.96 to −0.64); 0.019 | 26.1 (5.1) | −3.27 (−6.46 to −0.08); 0.045 | 27.5 (6.3) | −2.75 (−6.13 to 0.63); 0.11 | 26.6 (5.5) | −3.07 (−5.54 to −0.60); 0.015 |
| Term | 27.5 (5.6) | 25.2 (4.7) | −2.38 (−5.60 to 0.84); 0.15 | 25.4 (4.9) | −2.27 (−5.41 to 0.86); 0.15 | 25.8 (5.7) | −2.16 (−5.36 to 1.05); 0.18 | 25.9 (4.1) | −2.76 (−5.99 to 0.46); 0.09 | 25.6 (4.8) | −2.39 (−4.85 to 0.08); 0.06 |
| Duration of tube feeding (days); median (IQR) (geometric mean) | 7.0 (2.0, 13.0) (2.6) | 6.0 (3.5, 14.5) (5.6) | 1.67 (0.48 to 5.89); 0.42 | 13.0 (4.0, 15.0) (6.2) | 1.34 (0.39 to 4.68); 0.64 | 6.0 (1.0, 12.0) (2.5) | 0.77 (0.22 to 2.65); 0.68 | 13.5 (1.5, 17.5) (6.1) | 0.79 (0.23 to 2.70); 0.71 | 9.0 (2.0, 15.0) (3.4) | 1.07 (0.40 to 2.87); 0.89 |
| Length of stay (number of days); median (IQR) (geometric mean) | 9.0 (5.0, 15.0) (8.2) | 7.5 (6.5, 20.0) (8.6) | 1.06 (0.76 to 1.48); 0.73 | 15.0 (8.0, 18.0) (10.8) | 1.31 (0.94 to 1.83); 0.11 | 11.0 (6.0, 16.0) (10.5) | 1.29 (0.95 to 1.75); 0.10 | 14.0 (6.0, 20.0) (11.1) | 1.36 (0.98 to 1.87); 0.06 | 12.0 (6.0, 18.0) (10.3) | 1.26 (0.99 to 1.59); 0.06 |

*Number of infants with at least one anthropometric measurement at 2 weeks and term, respectively, are: 22 and 20 in placebo group; 21 and 19 in 5 mg/kg/day group; 26 and 21 in 10 mg/kg/day group; 21 and 19 in 15 mg/kg/day group and 22 and 18 in 20 mg/kg/day group.
†Growth velocity for weight was calculated using an exponential model[43] for weight and linear models for length, and head circumference.
‡Estimated group comparisons for failure to regain birth weight are ORs.
§Number of infants with feeding and sleeping data at 2 weeks and term, respectively, are: 22 and 20 in placebo group; 21 and 19 in 5 mg/kg/day group; 25 and 21 in 10 mg/kg/day group; 21 and 19 in 15 mg/kg/day group and 21 and 18 in 20 mg/kg/day group.
¶Sleep score was calculated using subscale nine on the Infant Behaviour Questionnaire-Revised, modified for neonates.[31]

**Table 4** Caffeine intake and salivary concentrations

| | Placebo N=24 | Caffeine citrate 5 mg/kg/day N=24 | Caffeine citrate 10 mg/kg/day N=27 | Caffeine citrate 15 mg/kg/day N=27 | Caffeine citrate 20 mg/kg/day N=28 | Any dose of caffeine N=106 |
|---|---|---|---|---|---|---|
| Maternal caffeine intake in preceding 24 hours (mg)* | | | | | | |
| Baseline | 36.3 (13.9, 83.2) | 63.3 (30.0, 115.6) | 65.2 (10.6, 116.4) | 42.3 (13.9, 67.7) | 41.6 (10.6, 142.0) | 51.5 (16.6, 105.0) |
| Two weeks | 60.5 (10.6, 87.5) | 84.1 (36.3, 110.4); p=0.064 | 39.5 (10.6, 144.8); p=0.675 | 36.3 (7.8, 78.8); p=0.752 | 88.2 (21.2, 175.0); p=0.099 | 63.5 (19.9, 115.6); p=0.252 |
| Term | 77.5 (41.8, 118.4) | 84.6 (60.5, 139.1); p=0.529 | 98.1 (15.5, 121.0); p=0.873 | 60.5 (36.3, 105.0); p=0.396 | 43.2 (10.6, 63.5); p=0.075 | 63.5 (21.2, 112.5); p=0.559 |
| Maternal salivary caffeine concentration at 2 weeks (µg/mL)† | 1.6 (0.5, 2.6) | 1.2 (0.6, 3.1); p=0.919 | 0.2 (0.0, 1.8); p=0.029 | 0.2 (0.0, 2.4); p=0.113 | 1.0 (0.2, 2.9); p=0.523 | 1.1 (0.1, 2.6); p=0.124 |
| Infant salivary caffeine concentration at 2 weeks (µg/mL)‡ | 0.6 (0.3, 0.9) | 17.6 (14.2, 23.8); p<0.001 | 26.1 (11.3, 36.3); p<0.001 | 33.7 (20.2, 51.0); p<0.001 | 71.0 (52.3, 86.5); p<0.001 | 28.3 (18.2, 52.3); p<0.001 |

Data presented are median (IQR).
*Number of mothers with completed surveys at baseline, 2 weeks and term, respectively, are: 23, 22 and 20 in placebo group; 23, 20 and 18 in 5 mg/kg/day group; 23, 22 and 19 in 10 mg/kg/day group; 25, 19 and 18 in 15 mg/kg/day group and 26, 18 and 18 in 20 mg/kg/day group.
†Number of mothers with salivary samples is 19 in placebo group; 16 in 5 mg/kg/day group; 21 in 10 mg/kg/day group; 17 in 15 mg/kg/day group and 14 in 20 mg/kg/day group.
‡Number of infants with salivary samples is 21 in placebo group; 18 in 5 mg/kg/day group; 20 in 10 mg/kg/day group; 18 in 15 mg/kg/day group and 16 in 20 mg/kg/day group.
§P values are from a Wilcoxon rank-sum test, due to highly skewed distributions.

overall compared with placebo (table 2). All secondary, sensitivity and exploratory analyses for the primary outcome gave similar results.

At 2 weeks postrandomisation, infants allocated to caffeine citrate 10 or 20 mg/kg/day, compared with placebo, had significantly higher mean $SpO_2$ and less time with $SpO_2$ <90%, while the 15 mg/kg/day group had higher mean heart rate. Compared with placebo, all caffeine groups spent significantly more time with tachycardia (heart rate >180 beats per min) at 2 weeks, which persisted at TEA in the 5, 10 and 20 mg/kg/day groups (table 2). At TEA, there were no significant differences between placebo and caffeine groups in the rate of IH, mean $SpO_2$ or time with $SpO_2$ <90% (table 2).

There was no difference between placebo and caffeine groups in the proportion of infants not regaining birth weight by 2 weeks, or in growth velocity for weight or length at any timepoint (table 3). Head circumference velocity was significantly lower in the 5 mg/kg/day group compared with placebo (table 3). Infants in the 20 mg/kg/day group, compared with placebo, had significantly lower length z-scores at 2 weeks and TEA (online supplemental table 1, online supplemental figures 1 and 2). Infants in the 10 and 15 mg/kg/day groups, compared with placebo, had significantly lower reflux symptom scores (Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R)) at 2 weeks (table 3). No infant required caffeine outside of the trial protocol. Eight infants (6%) received ongoing positive pressure support beyond randomisation, with no difference in rates between placebo and caffeine groups, and only one (15 mg/kg/day group) required respiratory support after enrolment (prior to administration of the study drug). There were no episodes of apnoea requiring stimulation after randomisation.

One infant (15 mg/kg/day group) was readmitted to hospital prior to 44 weeks' postmenstrual age due to an upper respiratory tract infection. There were no seizures or episodes of sepsis, nor neonatal or infant deaths. One infant (15 mg/kg/day group) had study drug stopped due to tachycardia at 2 weeks.

Infant salivary caffeine concentrations were higher in infants receiving caffeine, with highest concentrations in the 20 mg/kg/day group (table 4).

Fifteen infants across the four caffeine groups, but none in the placebo group, were withdrawn due to difficulties administering the study drug, the infant not tolerating the drug (spilling) or parental or investigator concerns about side effects (online supplemental table 3). The rate of stopping medication due to presumed side effects was not significantly different between the placebo and caffeine groups (table 2).

## DISCUSSION

In this randomised placebo-controlled dosage trial, caffeine citrate at 10 or 20 mg/kg/day reduced the mean rate of IH by 61% and 67%, respectively. Overall, caffeine did not have adverse effects on sleep, gastro-oesophageal reflux or feeding, although the percentage of time that infants had tachycardia increased, in keeping with previous reports.[34 35]

Currently, there is a lack of consensus definition for IH in preterm babies. We defined IH as $SpO_2$ fall ≥10% below baseline for <2 min, which previously we have shown to be increased in late preterm babies compared with term babies.[14] Although a 3% threshold is used in polysomnography to define desaturation events, a definition of 10% is commonly used in the neonatal literature,[36] and we considered this higher threshold more repeatable and reliable. We chose to include even short episodes

as these are believed to be as important as sustained hypoxaemia as a cause of subsequent neurocognitive deficits in children.[37 38]

The reason for a significant effect of caffeine citrate on the primary outcome at a dose of 10 and 20 but not 15 mg/kg/day is unclear. There were no differences in baseline characteristics to suggest confounding, and compliance with study medication was not worse in this group. Moreover, salivary caffeine concentration in the 15 mg/kg/day group was intermediate to that of the 10 and 20 mg/kg/day groups, and the percentage of the time these infants experienced tachycardia was comparable to the 20 mg/kg/day group, all of which indicate they received the study drug. Although the baseline rate of IH was higher in the 15 mg/kg/day group than in the 10 and 20 mg/kg/day groups, adjustment for this in secondary analysis did not alter results. It is possible that the lack of statistically significant reduction in IH in this group is due to type II error.

Both the 10 and 20 mg/kg/day doses were effective in late preterm infants as they reduced the rate of IH at 2 weeks, mean $SpO_2$ and time with $SpO_2$ <90%. This trial was powered to compare each caffeine citrate dose with placebo, rather than compare caffeine doses directly. However, the effect size in all respiratory measures was larger for the 20 mg/kg/day dose, with similar effects on drug tolerability to the 10 mg/kg/day dose. In addition, the 15 mg/kg/day dose was not effective, which would be expected if the 10 mg/kg/day dose was effective. Therefore, future trials in late preterm infants should consider using 20 mg/kg/day of caffeine citrate.

In the Caffeine for Apnea of Prematurity trial, very preterm infants receiving caffeine gained less weight than those in the placebo group during the first 3 weeks after randomisation, but there was no difference in weight by 4 weeks of age and no difference in head circumference.[39] In contrast, in our trial the only growth parameters affected by caffeine treatment were the length z-score, which was lower in the 20 mg/kg/day group at 2 weeks and TEA, and head circumference growth velocity, which was lower in the 5 mg/kg/day group. In both cases, a statistically significant difference occurred only in a single dose group and for a single parameter, and other related parameters failed to show the same changes; it thus appears unlikely that caffeine has a significant impact on overall neonatal growth.

A small observational study in low birthweight infants determined that the half-life of caffeine citrate is 86 hours at 34 weeks, reducing to 73 hours at 37 weeks and 6 hours at 60 weeks postmenstrual age.[22] In two other studies, caffeine citrate 6 mg/kg/day reduced IH at 35 and 36 weeks' gestational age,[24] but at 37 and 38 weeks' gestational age higher doses of 14 or 20 mg/kg/day were required to maintain caffeine salivary concentrations in the therapeutic range and reduce IH.[40] Our study supports the finding that higher doses of caffeine are required at later postmenstrual ages.

A limitation of this study was the higher rate of withdrawals in higher dose caffeine groups, mainly due to administration difficulties and poor tolerability. To maintain blinding, the trial drug was formulated at four different strengths, but at higher concentrations this resulted in a bitter solution, although one that is comparable to that used clinically. Unlike clinical use where very preterm infants receive caffeine citrate via a nasogastric tube, participating late preterm infants generally received the medication orally, meaning taste was important, and the volume was challenging to administer in some infants. Further trials on the use of caffeine citrate in the late preterm population should use a more palatable formulation. In addition, primary outcome data were not available for infants who were withdrawn prior to 2 weeks postrandomisation, and it is possible that attrition bias may have affected the outcome. However, it is unlikely that withdrawal from the study due to administration difficulties was linked to the primary outcome, so estimates of effectiveness should not have been affected by these withdrawals. A second limitation is that concurrent use of other medications was not formally recorded in this study. However, there are few clinically relevant drug interactions with caffeine citrate,[41] so it is unlikely that any participating infant received any medication that significantly affected plasma caffeine concentrations.

## CONCLUSION

Caffeine citrate reduces IH in late preterm infants, with doses of 10 and 20 mg/kg/day being effective, although difficult to administer to some babies in the current formulation, possibly due to the taste. Side effects at these doses include tachycardia, and possibly growth. A longer, larger trial with neurodevelopmental impairment as the primary outcome is required to establish if the reduction in IH will result in clinically significant improvements in neurodevelopment.

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**Contributors** JMA conceived and developed the study design, drafted the original study protocol, approved the final study protocol, reviewed the article for publication and is responsible for the accuracy and integrity of the data. EAO contributed to the study design, approved the final version of the study protocol and drafted the article for publication. CJDMK contributed to the study design, approved the final version of the study protocol and reviewed the article for publication. DMN contributed to the study design, approved the final version of the study protocol and reviewed the article for publication. AC contributed to and approved the final version of the statistical analysis plan, performed all statistical analyses and reviewed the article for publication.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by Health and Disability Ethics Committees of New Zealand (18/NTA/129). Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available on reasonable request. Published data are available to approved researchers under the data sharing arrangements provided by the Clinical Data Research Hub (CDRH), based at the Liggins Institute, University of Auckland (https://wiki.auckland.ac.nz/researchhub). Data access requests are to be submitted to the Data Access Committee via researchhub@auckland.ac.nz. Deidentified published data will be shared with researchers who provide a methodologically sound proposal and have appropriate ethical and institutional approval. Researchers must sign and adhere to the Data Access Agreement that includes a commitment to using the data only for the specified proposal, to refrain from any attempt to identify individual participants, to store data securely and to destroy or return the data after completion of the project. The CDRH reserves the right to charge a fee to cover the costs of making data available, if required.

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