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

Elizabeth Anne Oliphant 1,2, Christopher JD McKinlay 1,3, David McNamara 2, Alana Cavadino 1,4, Jane M Alsweiler 1,2

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 of caffeine citrate or placebo during the first 2 weeks of life.

Primary outcome IH (apnoea > 20 seconds and aim saturations < 93%) in the first 2 weeks post-randomisation.

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 post-randomisation (geometric mean (GM): 4.6, 4.6, 2.0, 2.0 and 2.0 events/hour for 0 mg/kg/day, 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 (SpO2) (97.2 (1.0) vs placebo 96.0 (0.8); p<0.001), and reduced median (IQR) percentage of time SpO2 <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.

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.

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, 4 developmental delay, 5,6 and cognitive impairment 7–13 compared with term infants. Late preterm infants also experience frequent episodes of intermittent hypoxaemia (IH), 14–16 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 (SpO2) significantly affect survival and neurodevelopment of very preterm infants 15,16 and transient intermittent hypoxaemic events are associated with poor neurodevelopmental outcomes in extremely preterm infants. 17

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. 22,23 and transient intermittent hypoxaemic events are associated with poor neurodevelopmental outcomes in extremely preterm infants. 18
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 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, SpO2 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 α=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 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 intake28 and infant feeding,29 sleeping30 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.12

Figure 1 Flow diagram of trial participants.
correct intervention and were compliant with the protocol\textsuperscript{18} (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

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=24*</th>
<th>Caffeine citrate 5mg/kg/day N=24*</th>
<th>Caffeine citrate 10mg/kg/day N=27*</th>
<th>Caffeine citrate 15 mg/kg/day N=27*</th>
<th>Any dose of caffeine N=105*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
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</tr>
<tr>
<td>Rate of intermittent hypoxaemia at 2 weeks median (IQR)</td>
<td>4.0 (1.8, 8.8)</td>
<td>5.9 (2.8, 7.6)</td>
<td>0.97 (0.49 to 1.96); p&lt;0.04</td>
<td>2.5 (0.6, 5.7)</td>
<td>1.8 (0.9, 4.2)</td>
</tr>
<tr>
<td>Mean difference(95% CI); p value†</td>
<td>0.94</td>
<td>0.39 (0.20 to 0.76); p&lt;0.006</td>
<td>3.3 (2.1, 8.8)</td>
<td>0.79 (0.40 to 1.56); p&lt;0.04</td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
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<tr>
<td>Rate of intermittent hypoxaemia; median (IQR) (geometric mean)</td>
<td>3.0 (1.3, 6.1)</td>
<td>2.7 (1.3, 6.1)</td>
<td>2.3 (1.1, 5.0)</td>
<td>1.5 (0.8, 2.4)</td>
<td>1.5 (0.8, 2.4)</td>
</tr>
<tr>
<td>Term</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>0.9 (0.6, 1.4)</td>
<td>2.0 (0.9, 3.3)</td>
<td>1.1 (0.7, 2.0)</td>
<td>1.9 (1.1, 3.6)</td>
<td>1.5 (0.8, 2.4)</td>
</tr>
<tr>
<td>Two weeks</td>
<td>3.0 (1.9, 6.2)</td>
<td>4.0 (1.9, 6.9)</td>
<td>2.5 (1.0, 6.1)</td>
<td>3.3 (1.5, 8.2)</td>
<td>2.2 (1.0, 4.7)</td>
</tr>
<tr>
<td>Mean SpO2; mean (SD)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>96.4 (1.3)</td>
<td>96.4 (1.5)</td>
<td>96.6 (1.8)</td>
<td>96.5 (1.4)</td>
<td>96.0 (1.7)</td>
</tr>
<tr>
<td>Two weeks</td>
<td>96.0 (0.8)</td>
<td>96.4 (1.4)</td>
<td>96.7 (1.0)</td>
<td>96.7 (1.3)</td>
<td>96.8 (1.2)</td>
</tr>
<tr>
<td>Term</td>
<td>97.2 (1.0)</td>
<td>97.7 (0.9)</td>
<td>97.2 (1.2)</td>
<td>97.4 (1.7)</td>
<td>97.3 (1.2)</td>
</tr>
<tr>
<td>Percentage of time SpO2 &lt;90%; median (IQR)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>1.1 (0.3, 1.6)</td>
<td>1.2 (0.5, 2.4)</td>
<td>1.2 (0.3, 1.9)</td>
<td>1.0 (0.6, 1.4)</td>
<td>1.5 (0.5, 3.3)</td>
</tr>
<tr>
<td>Two weeks</td>
<td>1.1 (0.6, 2.4)</td>
<td>1.0 (0.7, 2.0)</td>
<td>0.83 (0.43 to 1.60); p&lt;0.05</td>
<td>0.89 (0.43 to 1.84); p&lt;0.05</td>
<td></td>
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<tr>
<td>Term</td>
<td>0.6 (0.3, 1.1)</td>
<td>0.5 (0.3, 1.3)</td>
<td>0.6 (0.3, 1.3)</td>
<td>0.7 (0.3, 1.7)</td>
<td>0.6 (0.4, 1.3)</td>
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<tr>
<td>Mean heart rate; mean (SD)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>130.1 (8.0)</td>
<td>130.0 (6.8)</td>
<td>134.0 (12.7)</td>
<td>130.1 (9.3)</td>
<td>131.7 (9.3)</td>
</tr>
<tr>
<td>Two weeks</td>
<td>147.7 (6.8)</td>
<td>150.3 (8.2)</td>
<td>150.8 (7.4)</td>
<td>156.0 (12.7)</td>
<td>152.3 (12.4)</td>
</tr>
<tr>
<td>Term</td>
<td>150.8 (8.6)</td>
<td>150.3 (6.9)</td>
<td>152.3 (5.7)</td>
<td>155.5 (8.9)</td>
<td>151.8 (8.5)</td>
</tr>
<tr>
<td>Percentage of time HR &gt;180; median (IQR)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.4)</td>
<td>0.1 (0.0, 0.3)</td>
<td>0.0 (0.0, 0.3)</td>
<td>0.0 (0.0, 0.3)</td>
</tr>
<tr>
<td>Two weeks</td>
<td>0.9 (0.2, 5.2)</td>
<td>3.1 (2.0, 8.9)</td>
<td>4.3 (1.8)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td>2.0 (0.4, 5.6)</td>
<td>4.7 (3.0, 8.0)</td>
<td>5.5 (2.4, 9.4)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Compliant with administration schedule at 2 weeks</td>
<td>21 (87.5%)</td>
<td>18 (88.5%)</td>
<td>13 (66.7%)</td>
<td>19 (70.4%)</td>
<td></td>
</tr>
<tr>
<td>Study drug stopped due to presumed side effects</td>
<td>2.9 (1.1%)</td>
<td>4 (1.67%)</td>
<td>2.0 (0.32 to 13.18); 0.44</td>
<td>5 (19.2%)</td>
<td></td>
</tr>
</tbody>
</table>
| *Number of infants with olfactory function (8% of total remaining in study at that group) at baseline, 2 weeks and term, respectively are 20 (83.3%), 22 (90.2%), 20 (86.7%) in placebo group; 21 (90.9%), 20 (100%), 18 (94.7%) in 5 mg/kg/day group; 26 (96.3%), 24 (96.4%), 20 (99.2%) in 10 mg/kg/day group; 27 (100%), 21 (100%), 18 (94.7%) in 15 mg/kg/day group and 25 (99.9%), 20 (100%), 17 (95.9%) in 20 mg/kg/day group.† Where the median (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 derived as <50% or 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 weeks visit (ie, >20% 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

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=24*</th>
<th>Caffeine citrate 5 mg/kg/day N=24</th>
<th>Caffeine citrate 10 mg/kg/day N=27</th>
<th>Caffeine citrate 15 mg/kg/day N=27</th>
<th>Caffeine citrate 20 mg/kg/day N=27</th>
<th>Any dose of caffeine N=105</th>
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<tbody>
<tr>
<td></td>
<td>Summary data</td>
<td>Summary data</td>
<td>Summary data</td>
<td>Summary data</td>
<td>Summary data</td>
<td>Summary data</td>
</tr>
<tr>
<td>Weight growth velocity (birth to term equivalent) (g/kg/day)</td>
<td>8.8 (3.1)</td>
<td>8.4 (3.4)</td>
<td>−0.45 (−2.25 to 1.65); 0.67</td>
<td>7.5 (3.4)</td>
<td>9.1 (3.4)</td>
<td>0.02 (−2.10 to 2.15); 0.98</td>
</tr>
<tr>
<td>Length growth velocity (birth to term equivalent) (cm/week)</td>
<td>0.7 (0.6)</td>
<td>0.7 (0.4)</td>
<td>−0.03 (−0.39 to 0.23); 0.61</td>
<td>0.7 (0.6)</td>
<td>1.0 (0.4)</td>
<td>0.20 (−0.11 to 0.52); 0.20</td>
</tr>
<tr>
<td>Head circumference growth velocity (birth to term equivalent) (cm/week)</td>
<td>0.6 (0.3)</td>
<td>0.4 (0.2)</td>
<td>−0.23 (−0.40 to −0.07); 0.006</td>
<td>0.5 (0.3)</td>
<td>0.5 (0.2)</td>
<td>−0.01 (−0.33 to 0.00); 0.05</td>
</tr>
<tr>
<td>Failure to regain birth weight by 2 weeks postnatal age; %</td>
<td>2 (8.3%)</td>
<td>2 (8.3%)</td>
<td>0.0 (−2.25 to 2.15); 0.98</td>
<td>1.91 (0.28, 13.29); 0.15</td>
<td>9.4 (2.72 to 26.16); 0.11</td>
<td>3.50 (0.55 to 22.30); 0.18</td>
</tr>
<tr>
<td>Sleep score; mean (SD)§,¶</td>
<td>4.2 (0.6)</td>
<td>4.3 (0.3)</td>
<td>0.11 (−0.17 to 0.38); 0.45</td>
<td>4.3 (0.5)</td>
<td>4.2 (0.3)</td>
<td>0.01 (−0.27 to 0.29); 0.87</td>
</tr>
<tr>
<td>Gastro-oesophageal symptoms; I-GERQ-R mean (SD)§</td>
<td>29.7 (4.3)</td>
<td>27.6 (4.2)</td>
<td>−2.35 (−5.56 to 0.85); 0.15</td>
<td>25.3 (6.1)</td>
<td>26.1 (5.1)</td>
<td>−3.17 (−6.46 to −0.08); 0.085</td>
</tr>
<tr>
<td>Duration of tube feeding (days); median (IQR) (geometric mean)</td>
<td>7.0 (2.0, 13.0) (2.6)</td>
<td>6.0 (3.5, 14.5) (5.6)</td>
<td>1.67 (0.48 to 5.89); 0.015</td>
<td>13.0 (4.0, 15.0) (6.2)</td>
<td>13.0 (4.0, 15.0) (6.2)</td>
<td>1.34 (0.39 to 4.48); 0.64</td>
</tr>
<tr>
<td>Length of stay (number of days); median (IQR) (geometric mean)</td>
<td>9.0 (5.0, 15.0) (8.2)</td>
<td>7.5 (6.5, 20.0) (8.6)</td>
<td>1.06 (0.76 to 1.48); 0.73</td>
<td>15.0 (8.0, 18.0) (10.8)</td>
<td>11.0 (6.0, 16.0) (10.5)</td>
<td>1.29 (0.95 to 1.75); 0.10</td>
</tr>
</tbody>
</table>

*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 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

<table>
<thead>
<tr>
<th>Maternal caffeine intake in preceding 24 hours (mg)*</th>
<th>Placebo N=24</th>
<th>Caffeine citrate 5 mg/kg/day N=28</th>
<th>Caffeine citrate 10 mg/kg/day N=27</th>
<th>Caffeine citrate 15 mg/kg/day N=27</th>
<th>Caffeine citrate 20 mg/kg/day N=28</th>
<th>Any dose of caffeine N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>36.3 (13.9, 83.2)</td>
<td>63.3 (30.0, 115.6)</td>
<td>65.2 (10.6, 116.4)</td>
<td>42.3 (13.9, 67.7)</td>
<td>41.6 (10.6, 142.0)</td>
<td>51.5 (16.6, 105.0)</td>
</tr>
<tr>
<td>Two weeks</td>
<td>60.5 (10.6, 87.5)</td>
<td>84.1 (36.3, 110.4); p=0.064</td>
<td>39.5 (10.6, 144.8); p=0.675</td>
<td>36.3 (7.8, 78.8); p=0.752</td>
<td>88.2 (12.1, 175.0); p=0.099</td>
<td>63.5 (19.9, 115.6); p=0.252</td>
</tr>
<tr>
<td>Term</td>
<td>77.5 (41.8, 118.4)</td>
<td>84.6 (60.5, 139.1); p=0.529</td>
<td>98.1 (15.5, 121.0); p=0.873</td>
<td>60.5 (36.3, 105.0); p=0.396</td>
<td>43.2 (10.6, 63.5); p=0.752</td>
<td>63.5 (12.1, 112.5); p=0.559</td>
</tr>
<tr>
<td>Maternal salivary caffeine concentration at 12 weeks (μg/mL)†</td>
<td>1.6 (0.5, 2.6)</td>
<td>1.2 (0.6, 3.1); p=0.019</td>
<td>0.2 (0.0, 1.8); p=0.029</td>
<td>0.2 (0.0, 2.4); p=0.113</td>
<td>1.0 (0.2, 2.9); p=0.523</td>
<td>1.1 (0.1, 2.6); p=0.124</td>
</tr>
<tr>
<td>Infant salivary caffeine concentration at 2 weeks (μg/mL)‡</td>
<td>0.6 (0.3, 0.9)</td>
<td>17.6 (14.2, 23.8); p&lt;0.001</td>
<td>26.1 (11.3, 36.3); p&lt;0.001</td>
<td>33.7 (20.2, 51.0); p&lt;0.001</td>
<td>71.0 (52.3, 86.5); p&lt;0.001</td>
<td>28.3 (18.2, 52.3); p&lt;0.001</td>
</tr>
</tbody>
</table>

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, 22 and 19 in 5 mg/kg/day group; 15 and 18 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.

DISCUSSION

In the randomised placebo-controlled dosage trial, caffeine citrate at 10 or 20 mg/kg/day reduced the mean rate of IH events, a definition of 10% is commonly used in the neonatal literature, and we considered this higher threshold more meaningful. We defined IH as SpO2 <90% (table 2). All secondary, sensitivity and exploratory analyses for the primary outcome gave similar results.

At 2 weeks post-randomisation, infants allocated to caffeine citrate 15 or 20 mg/kg/day, compared with placebo, had significantly lower reflux symptom scores (table 3). Infants in the 15 mg/kg/day group, compared with placebo and caffeine citrate 20 mg/kg/day, had significantly lower reflux symptom scores (table 2).

There was no difference between placebo and caffeine citrate groups in the proportion of infants not regaining birth weight and growth velocity for weight or length at any timepoint (table 3). Infants in the 15 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 (table 3). Infants in the 20 mg/kg/day group, compared with placebo, had significantly lower reflux symptom scores (table 2).

There was no difference between placebo and caffeine citrate groups in the rate of IH, mean SpO2 or time spent with SpO2 <90% (table 3). Head circumference velocity was significantly lower in the 5, 10 and 20 mg/kg/day groups compared with placebo and caffeine citrate groups in the rate of IH, mean SpO2 or time spent with SpO2 <90% (table 3). There were no significant differences between placebo and caffeine citrate groups in the rate of IH, mean SpO2 or time spent with SpO2 <90% (table 3). At TEA, there were no significant differences between placebo and caffeine citrate groups in the rate of IH, mean SpO2 or time spent with SpO2 <90% (table 3).
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 \(\text{SpO}_2\) and time with \(\text{SpO}_2 < 90\%\). 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 difference in head circumference. 39 In contrast, in our trial the infants receiving caffeine gained less weight than those in the therapeutic range and reduce IH.40 Our study supports the finding that higher doses of caffeine are required at later gestation, and our results indicate that 10 mg/kg/day might 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.

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.

Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY.

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Supplemental material

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ORCID iDs

Elizabeth Anne Oliphant http://orcid.org/0000-0002-3660-4127
Christopher JD McNamara http://orcid.org/0000-0003-1088-9467
David McNamara http://orcid.org/0000-0002-4302-8746
Alana Cavadino http://orcid.org/0000-0002-5709-367X
Jane M Alsewiler http://orcid.org/0000-0002-0874-6654

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