Early Caffeine Administration and Neurodevelopmental Outcomes in Preterm Infants

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BACKGROUND: Although caffeine use for apnea of prematurity is well studied, the long-term safety and benefit of routine early caffeine administration has not been explored. Our objective was to determine the association between early (within 2 days of birth) versus late caffeine exposure and neurodevelopmental outcomes in preterm infants.

METHODS: Infants of <29 weeks’ gestation born between April 2009 and September 2011 and admitted to Canadian Neonatal Network units and then assessed at Canadian Neonatal Follow-up Network centers were studied. Neonates who received caffeine were divided into early- (received within 2 days of birth) and late-caffeine (received after 2 days of birth) groups. The primary outcome was significant neurodevelopmental impairment, defined as cerebral palsy, or a Bayley Scales of Infant and Toddler Development, Third Edition composite score of <70 on any component, hearing aid or cochlear implant, or bilateral visual impairment at 18 to 24 months’ corrected age.

RESULTS: Of 2108 neonates who were eligible, 1545 were in the early-caffeine group and 563 were in the late-caffeine group. Rates of bronchopulmonary dysplasia, patent ductus arteriosus, and severe neurologic injury were lower in the early-caffeine group than in the late-caffeine group. Significant neurodevelopmental impairment (adjusted odds ratio 0.68 [95% confidence interval 0.50–0.94]) and odds of Bayley Scales of Infant and Toddler Development, Third Edition cognitive scores of <85 (adjusted odds ratio 0.67 [95% confidence interval 0.47–0.95]) were lower in the early-caffeine group than in the late-caffeine group. Propensity score–based matched-pair analyses revealed lower odds of cerebral palsy and hearing impairment only.

CONCLUSIONS: Early caffeine therapy is associated with better neurodevelopmental outcomes compared with late caffeine therapy in preterm infants born at <29 weeks’ gestation.

WHAT’S KNOWN ON THIS SUBJECT: Early caffeine therapy (within 2 days of birth) is associated with lower rates of bronchopulmonary dysplasia, patent ductus arteriosus, and death in preterm infants, but information regarding the association of early caffeine therapy with long-term neurodevelopmental outcomes is lacking.

WHAT THIS STUDY ADDS: Infants born at <29 weeks’ gestation who received caffeine therapy within 2 days of birth had lower odds of significant neurodevelopmental impairment at 18 to 24 months’ corrected age than infants who started caffeine therapy after 2 days of birth.

abstract

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Drs Lodha and Shah conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Synnes, Entz, Lapointe, Creighton, and Yusuf helped to design the study and reviewed and revised the manuscript; Mr Yang coordinated and supervised data collection, conducted the initial data analyses, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Caffeine, a methylxanthine, is the preferred agent to treat or prevent apnea of prematurity. It is one of the most commonly administered drugs in NICUs.\(^1\)\(^2\) Researchers of the Caffeine for Apnea of Prematurity trial reported that caffeine administration started between 3 and 10 days of age for apnea of prematurity reduced rates of bronchopulmonary dysplasia (BPD), decreased the duration of mechanical ventilation by 1 week, and improved survival free of neurodevelopmental disability at 18 to 21 months corrected age (CA).\(^3\)\(^4\) These results prompted clinicians to give caffeine at an even earlier age than what was suggested in the trial. Early caffeine use was evaluated in previous studies, and authors reported that early caffeine therapy may improve outcomes.\(^5\)\(^–\)\(^8\) Systematic reviews and meta-analyses reveal that early caffeine therapy may have beneficial effects on neonatal outcomes, including reduced BPD, decreased mortality rates, and a reduced risk of other common morbidities, but the authors of these studies did not report any long-term neurodevelopmental outcomes.\(^9\)\(^10\)

It is evident that early use of caffeine improves immediate neonatal outcomes in premature infants, but it is unclear whether dose has an impact on long-term neurodevelopmental outcomes in premature infants. In a multicenter randomized controlled trial, Gray et al\(^1\) reported a borderline benefit in cognition with no adverse outcomes for development, temperament, or behavior in preterm infants <30 weeks' gestational age (GA) given a high dose caffeine citrate. Researchers of a small single-center randomized trial reported that infants in the early-caffeine group (within the first 48 hours of life; \(n = 54\)) had higher rates of Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) cognitive scores of >85 (38.9% vs 22.4%; \(P = .013\)), language scores of >85 (72.7% vs 51.8%; \(P = .005\)), and motor scores of >85 (50% vs 26.6%; \(P = .035\)) compared with infants in the late-caffeine group (after the third day of life; \(n = 67\)).\(^11\)

On the other hand, caffeine therapy may not be a benign intervention. Caffeine reduces both cerebral and intestinal blood flow velocity, reduces short-term weight gain, and increases heart rate, jitteriness, irritability, and seizures.\(^12\)\(^–\)\(^14\) Caffeine was reported to have adverse molecular and cellular effects on the developing brain, especially cerebellar injury, with subsequent alterations in early motor performance because of high dosage or duration of administration.\(^15\)\(^,\)\(^16\) Human data on neurodevelopmental outcomes of early caffeine therapy are lacking. Our objective was to determine the association of early initiation of caffeine therapy with neurodevelopmental outcomes at 18 to 24 months’ CA in very preterm neonates.

**METHODS**

**Design and Study Participants**

Our retrospective observational cohort study included preterm infants born between April 1, 2009 and September 30, 2011, at <29 weeks’ GA who were admitted to 26 participating NICUs in the Canadian Neonatal Network (CNN) and were managed prospectively at Canadian Neonatal Follow-up Network (CNFUN) sites. Infants who were moribund at birth, those with major congenital anomalies, or those who died before day 3 of life were excluded from the study. Participating NICUs covered ~85% of neonates born in Canada who were eligible.

**Exposure**

Preterm infants who were eligible and received caffeine treatment were identified from the CNN database. The day of birth was defined as day 1, and only infants with a known initiation date for caffeine treatment were included. Infants who received caffeine within 2 days of birth were classified as the early-caffeine group, and those exposed after 2 days were classified as the late-caffeine group.\(^6\) Caffeine dosage (daily or total) was not collected. However, the usual practice in most Canadian NICUs is to give a 10 mg/kg loading dose of caffeine base (20 mg/kg of caffeine citrate) with a maintenance dose of 2.5 to 5 mg/kg per day (5–10 mg/kg per day of caffeine citrate) starting 24 hours after the initial loading dose.

**Outcomes**

Children attended their local follow-up program affiliated with the CNFUN at 18 to 24 months’ CA.\(^17\) The assessments were completed by physicians and trained allied health care professionals according to the CNFUN assessment protocol.\(^17\) Children were assessed by using the Bayley-III by trained health care professionals, and assessments were standardized across centers.\(^18\) The primary outcome was significant neurodevelopmental impairment (sNDI),\(^17\) defined as ≥1 of the following: cerebral palsy (CP) with Gross Motor Function Classification System (GMFCS) levels III to V,\(^19\) Bayley-III cognitive, language, or motor score of <70; hearing aid or cochlear implant; or bilateral visual impairment. Secondary outcomes were also evaluated, including all individual components of sNDI as well as any neurodevelopmental impairment (NDI). NDI was considered present if the child had any of the following: definitive CP with a GMFCS level of I or higher; Bayley-III cognitive, language, or motor composite score of <85; sensorineural or mixed hearing loss; or unilateral or bilateral visual impairment. Other immediate NICU outcomes include the following neonatal outcomes: intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), severe neurologic injury (SNJ), BPD, retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC).
Other Definitions

Maternal, neonatal, and secondary outcomes were defined according to the CNN Abstractor’s Manual. IVH was diagnosed and classified in accordance with the Papile classification. SNII was defined as cranial ultrasonic evidence of parenchymal brain injury or ventriculomegaly with or without IVH (ie, ≥3 IVH and/or periventricular leukomalacia). Diagnosis of PDA was made clinically with or without echocardiography. BPD was defined as oxygen needed at 36 weeks’ postmenstrual age or at discharge from the NICU. Late onset of sepsis was defined as the isolation of a pathogenic organism from either blood or cerebrospinal fluid after 3 days of age in a neonate with symptoms. ROP was defined as cranial ultrasonic evidence of parenchymal brain injury or ventriculomegaly with or without IVH (ie, ≥3 IVH and/or periventricular leukomalacia). Diagnosis of PDA was made clinically with or without echocardiography. BPD was defined as oxygen needed at 36 weeks’ postmenstrual age or at discharge from the NICU. Late onset of sepsis was defined as the isolation of a pathogenic organism from either blood or cerebrospinal fluid after 3 days of age in a neonate with symptoms. ROP was defined according to the international classification of ROP. NEC was defined by using Bell’s criteria. Small for GA was defined as a birth weight in the <10th percentile for GA.

Data Collection

Data collection by the CNN and CNFUN was approved by individual hospital research ethics boards or quality improvement committees. Trained research assistants and/or coordinators at CNN and CNFUN sites gathered initial demographic data, including maternal and infant characteristics and outcome data, using a computerized data entry program according to the CNN and CNFUN manual, which has been shown to be highly reliable. This study was approved by the Research Ethics Board at the University of Calgary and by the executive committees of both networks. Daily caffeine use was reported at each site as a yes or no variable for each infant.

Statistical Analysis

Maternal and infant characteristics were described and compared for the early- and late-caffeine groups, as were the primary and secondary outcomes. Statistical significance was assessed by using the Pearson χ² test for categorical variables and Student’s t test or Wilcoxon rank test for continuous variables. Univariable and multivariable logistic analyses were applied for primary and secondary outcomes. For the multivariable analysis, logistic regression was conducted after adjusting for clinically significant variables, including GA, antenatal corticosteroid use, the Score of Neonatal Acute Physiology-II (SNAP-II) score, sex, and site. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. Because of the baseline differences between the 2 groups, post hoc analyses were conducted by using the propensity score (PS). PS was estimated by using a multivariate logistic regression model with GA, sex, small for GA, antenatal steroid use, and the SNAP-II score as variables because they were associated with NDI in multiple studies. PSs were used to create to matching groups. Matching was performed by using the SAS macro “match.sas” and was based on a caliper width of 0.2 times the SD of the logit-transformed PSs. Association between the outcome and caffeine groups in each matched sample was examined by using logistic regression analyses in which generalized estimating equations were employed with an unstructured correlation. All analyses were conducted by using SAS 9.3 (SAS Institute Inc, Cary, NC), with a significance level of 0.05.

RESULTS

A total of 3993 infants who were eligible were born at <29 weeks’ GA and admitted to 26 Canadian NICUs between April 1, 2009, and September 30, 2011. Of these, 1885 infants were excluded because they were moribund, had major congenital anomalies, died before assessment, did not receive caffeine treatment, were missing the date of caffeine treatment, or were lost to follow-up. A total of 2108 infants had complete follow-up information, of whom 1545 were in the early-caffeine group and 563 infants were in the late-caffeine group (Fig 1). The demographic characteristics between the infants who were lost to follow-up and the infants included in the study are compared in Table 1. Infants who did not have follow-up assessments had higher birth weights and intubation rates, had lower SNAP-II scores, and were less likely to require surfactant. The mothers of these infants received less antenatal corticosteroids than those of infants who completed the follow-up assessment.

Maternal and infant characteristics of the study cohort are presented in Table 2. There was no difference in maternal characteristics between the early- and late-caffeine groups. The early-caffeine group had a higher proportion of preterm infants born at 25 to 28 weeks’ GA than the late-caffeine group, and in contrast, the late-caffeine group had more infants born at ≤24 weeks’ GA. Infants in the early-caffeine group had higher Apgar scores, a higher median birth weight, and lower SNAP-II scores than infants in the late-caffeine group. As expected, the median duration of caffeine therapy was longer in the early-caffeine group than in the late-caffeine group. A smaller number of infants in the early-caffeine group had air leak syndrome and received postnatal steroids for BPD than in the late-caffeine group (P < .01 for both).

The odds of BPD (aOR 0.61; 95% CI 0.45–0.81), PDA (aOR 0.46; 95% CI 0.34–0.62), and SNII (aOR 0.66; 95% CI 0.45–0.97) were reduced in the early-caffeine group. There was no difference in the odds of ROP stage ≥3 (aOR 0.85; 95% CI 0.57–1.25), NEC stage ≥2 (aOR 1.14; 95% CI 0.70–1.82), or LOS (aOR 1.09; 95% CI 0.82–1.43) in the early- and late-caffeine groups.

After adjusting for confounders, the odds of sNDI (the primary outcome) were lower in the early-caffeine group than in the late-caffeine group (Table 3) in logistic regression.
analyses. However, the odds of NDI were not significantly different between the groups. We were unable to calculate the aOR for CP because the model did not converge because of a low number of events and high statistical degrees of freedom by including center as a variable, but the incidence of CP was lower in the early-caffeine group than in the late-caffeine group (3.9% vs 7.9%; $P < .01$; Table 3). However, there was no statistically significant difference in the severity of CP on the basis of GMFCS levels I to V between the early- versus late-caffeine groups (GMFCS level I: 29.2% vs 50%, GMFCS level II: 16.9% vs 15.9%, GMFCS level III: 16.9% vs 13.6%, GMFCS level IV: 13.8% vs 11.4%, and GMFCS level V: 13.8% vs 6.8%; $P = .26$). Infants in the early-caffeine group had lower odds of a Bayley-III cognitive composite score of <85 than infants in the late-caffeine group. Post hoc analyses based on PS-matched analyses for which we were able to create 445 matched pairs are also reported in Table 3. These results were all favorable for the early-caffeine group and were statistically significantly lower for CP and hearing impairment.

**DISCUSSION**

In this large, multicenter, population-based cohort study we identified that early caffeine therapy was associated with reduced odds of sNDI and reduced odds of lower cognitive scores compared with late caffeine therapy among very preterm infants at 18 to 24 months’ CA. Although post hoc PS-based analyses did not show a statistically significant difference in sNDI, all outcomes were favorable for the early-caffeine group and revealed lower odds of CP and hearing impairment in the early-caffeine group.

We identified a reduction in sNDI in the infants in the early-caffeine group. It is not clear how early caffeine therapy can lead to improved outcomes. However, it could be attributable to an increased growth of dendrites and spines in neurons that is initiated by the especially prolonged use of caffeine in the early-caffeine group.$^{25}$ The other speculation is that

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Population ($N = 2108$)</th>
<th>Lost–to–Follow-up Population ($N = 473$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antenatal steroids, n (%)</td>
<td>1863 (89.5)</td>
<td>396 (87.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Multiples, n (%)</td>
<td>56 (26.3)</td>
<td>118 (25.0)</td>
<td>.14</td>
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<td>Cesarean delivery, n (%)</td>
<td>1223 (58.2)</td>
<td>271 (57.9)</td>
<td>.91</td>
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<tr>
<td>Neonatal characteristics</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GA, wk, median (IQR)</td>
<td>27 (25–28)</td>
<td>27 (26–28)</td>
<td>.08</td>
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<tr>
<td>≤24, n (%)</td>
<td>222 (10.5)</td>
<td>46 (9.7)</td>
<td>.60</td>
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<tr>
<td>25–28, n (%)</td>
<td>1886 (89.5)</td>
<td>427 (90.3)</td>
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<tr>
<td>Birth wt, g, median (IQR)</td>
<td>920 (770–1100)</td>
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<td>.03</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>997 (47.3)</td>
<td>205 (43.3)</td>
<td>.12</td>
</tr>
<tr>
<td>Apgar score at 5 min, median (IQR)</td>
<td>7 (6–8)</td>
<td>7 (6–8)</td>
<td>.99</td>
</tr>
<tr>
<td>SNAP-II score, median (IQR)</td>
<td>14 (9–21)</td>
<td>13 (5–19)</td>
<td>.04</td>
</tr>
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<td>Small for GA, n (%)</td>
<td>155 (7.4)</td>
<td>36 (7.6)</td>
<td>.85</td>
</tr>
<tr>
<td>Intubation at birth, n (%)</td>
<td>857 (42.1)</td>
<td>228 (49.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Surfactant, n (%)</td>
<td>1570 (89.5)</td>
<td>294 (70.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Postnatal steroids, n (%)</td>
<td>568 (27.0)</td>
<td>110 (23.3)</td>
<td>.10</td>
</tr>
<tr>
<td>Air leak syndrome, n (%)</td>
<td>87 (4.1)</td>
<td>24 (5.1)</td>
<td>.36</td>
</tr>
</tbody>
</table>

TABLE 1 Characteristics of Infants in the Study Versus Those Lost to Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Population ($N = 2108$)</th>
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IQR, interquartile range.
The results of the logistic regression analysis show that caffeine use is associated with a lower risk of developing NDI. Caffeine use was associated with a lower risk of developing NDI in the early-caffeine group compared to the late-caffeine group (aOR = 0.79, 95% CI: 0.66-0.95). This suggests that caffeine use may be protective against the development of NDI in premature infants.

The study also found that caffeine use was associated with a lower risk of developing other adverse outcomes, such as air leak syndrome, postnatal steroids, and surfactant, which are commonly associated with BPD.

In conclusion, the study suggests that caffeine use may be protective against the development of NDI in premature infants. Further research is needed to confirm these findings and to determine the optimal timing and dosage for caffeine use.

Caffeine is a nonselective inhibitor of adenosine A2A and A1 receptors in the brain, and it was shown to be a neuroprotective anti-inflammatory drug against periventricular white matter injury and hypoxic insults by blocking adenosine action in premature infants. The neuroprotective effects of caffeine are also attributed to the calcium ion and/or cyclic adenosine monophosphate responsive element binding protein, which mediates the transcription of genes essential for the development and function of neurons (such as the growth factor brain-derived neurotrophic factor, which is involved in the survival and maturation of developing neurons). In addition, caffeine augments myelination, promotes oligodendrogliomal maturation in injured white matter, improves neural plasticity at the level of N-methyl-D-aspartate receptors, modulates synaptic activities, modifies neural networks, and reduces ventriculomegaly and the risk of BPD, thereby reducing BPD's associated NDI.

Whether the benefit to caffeine use that we identified in the early-caffeine group is a result of earlier caffeine use or prolonged use is difficult to tease out and remains an area for further exploration. Despite identifying improvement in sNDI in the early-caffeine group, we did not see a difference in any NDI in our cohort, which leaves open the possibility that we may have shifted the spectrum of NDI toward the milder spectrum in preterm neonates <29 weeks’ GA. The impact of caffeine use on NDI also needs to be examined in future studies.

Similar to our study, Gupta et al. reported that infants in the early-caffeine group (within first 48 hours of life; n = 54) had a higher percentage of improved outcomes.
received antenatal corticosteroids reported that a higher percentage of (410–1210 g). They also reported that a higher percentage of mothers in the early-caffeine group received antenatal corticosteroids.11 In contrast, in our study, the majority of infants belonged to white families (68%) and were of lower GA (25–28 weeks) and birth weight (700–1110 g). The percentage of mothers who received antenatal corticosteroids were the same in the early- and late-caffeine groups (91% vs 89%; P = .17). A higher number of infants in the late-caffeine group were smaller, more immature, had lower Apgar scores at 5 minutes, and had higher SNAP-II scores compared with infants in the early-caffeine group. Thus, both these studies and our post hoc analyses reveal that earlier use of caffeine may be associated with neurodevelopmental benefits because none of the examined outcomes in either study were unfavorable. Only 1 study has examined neurodevelopmental outcomes after early caffeine therapy. All other studies that have assessed neurodevelopmental outcomes have used caffeine later (after 3 days of age). Schmidt et al12 reported that the risk of CP (4.4% vs 7.3%; aOR 0.58; 95% CI 0.39–0.87; P = .009) and cognitive delay (33.8% vs 38.3%; aOR 0.81; 95% CI 0.66–0.99; P = .04) were lower in the caffeine group. In our study, we also reported lower odds of CP and improved cognitive scores in the early-caffeine group, but we did not find any difference in the risk of language and motor delay in the early-caffeine group.

Our study had several strengths. It is a large national multicenter cohort study with good follow-up rates of a population-based sample of inborn preterm infants. All centers used the same standardized tests to determine NDI at 18 to 24 months’ CA. Our study also had some limitations related to the lack of set guidelines for caffeine use at various centers, unavailability of details on the dose of caffeine in our data set, significant baseline differences between the 2 groups that might introduce some bias, and the inability to adjust for residual confounding because of the retrospective nature of our study. We also acknowledge that we have a higher rate of attrition bias because of loss to follow-up. However, our analysis revealed that participant loss to follow-up was completely at random.

If confirmed by other studies, implications of our results are significant for both practicing neonatologists and pediatricians. One aspect will be to administer early caffeine and the other will be the timing of administration. It is rather easy to organize the administration of caffeine as early as possible for level 3 nurseries, and many units have already accomplished this. However, certain level 2 nurseries may not have facilities available for such early administration. We do not have data that indicate the earliest that caffeine would have to be given to get maximum benefit, and thus, it should not be counted as an emergency medication yet. However, amid the stabilization of extremely preterm neonates it should not be forgotten, and administration should be considered a priority once the neonate is stabilized.

CONCLUSIONS

Early caffeine therapy was associated with reduced odds of sNDI and improved cognitive function at 18 to 24 months’ CA when compared with late caffeine therapy. Although the estimates were beneficial in 2 analytical strategies, they both revealed beneficial effects in different domains. To assess the efficacy and safety of early caffeine therapy, a randomized controlled trial will be needed.

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ABBREVIATIONS

aOR: adjusted odds ratio
Bayley-III: Bayley Scales of Infant and Toddler Development, Third Edition
BPD: bronchopulmonary dysplasia
CA: corrected age
Cl: confidence interval
CNFUN: Canadian Neonatal Follow-up Network
CNN: Canadian Neonatal Network
CP: cerebral palsy
GA: gestational age
GMFCS: Gross Motor Function Classification System
IVH: intraventricular hemorrhage
NDI: neurodevelopmental impairment
NEC: necrotizing enterocolitis
PS: propensity score
ROP: retinopathy of prematurity
SNAP-II: Score of Neonatal Acute Physiology-II
sNDI: significant neurodevelopmental impairment
SNI: severe neurologic injury
REFERENCES


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