Journal of Perinatology (2018) 38:889–899
https://doi.org/10.1038/s41372-018-0106-y

ARTICLE

Does duration of caffeine therapy in preterm infants born ≤1250 g at birth influence neurodevelopmental (ND) outcomes at 3 years of age?

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Received: 27 October 2017 / Revised: 28 February 2018 / Accepted: 6 March 2018 / Published online: 8 May 2018

Abstract

Objective: To evaluate the effect of duration of caffeine use on long-term neurodevelopmental (ND) outcomes at 3 years corrected age (CA) in preterm infants with birthweights (BW) ≤ 1250 g.

Design/Methods: All surviving infants with BW ≤ 1250 g admitted to the Foothills Medical Center neonatal intensive care unit (NICU) from January 2002 to December 2009 who received the first dose of caffeine in the first week of life and were followed up at three years CA were included in the study. Demographics and follow-up outcomes were compared based on early cessation of caffeine ≤ 14 days (ECC), intermediate cessation of caffeine 15–30 days (ICC), and late cessation of caffeine >30 days (LCC). The primary outcome of ND impairment was present if a child had any one of the following: cerebral palsy, cognitive delay, visual impairment, or hearing impairment or deafness. Univariate and logistic regression analyses were performed.

Results: Of the 508 eligible infants, 448 (88%) were seen at 3 years CA at follow-up. ECC ($n = 139$), ICC ($n = 122$) and LCC ($n = 187$) groups had a median (range) BW of 979 (560–1250), 1010 (530–1250), and 980 (520–1250) g ($p = 0.524$) and median (range) gestational age (GA) of 27 (23–33), 28 (24–33), and 27 (24–32) weeks, respectively ($p = 0.034$). In logistic regression models adjusting for GA, maternal smoking, and each neonatal risk factor separately (IVH, NEC, sepsis, blood transfusions, BPD, postnatal dexamethasone, SNAP-II, and ventilator days), none of the models showed a statistically significant association between caffeine duration and ND impairment.

Conclusion: The duration of caffeine use in premature infants in the NICU does not impact on long-term ND outcomes at 3 years CA.

Introduction

Apnea of prematurity (AOP) is a common complication in preterm neonates [1, 2]. Caffeine, a methylxanthine, is an effective drug to treat AOP [2, 3] and has been shown to be one of the most common medications used in neonatal intensive care units (NICUs) [4]. Evidence for the benefits of caffeine therapy on neonatal outcomes is overwhelming, with studies showing prevention of bronchopulmonary dysplasia (BPD), as well as reduction in the incidence of other neonatal complications such as respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH) and AOP [3, 5–7].

Methylxanthines are antagonists of adenosine receptors [8]. Although adenosine has been shown to protect the brain from hypoxia and ischemia in certain animal models [9, 10],

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caffeine has also demonstrated a neuroprotective effect on the developing brain in both animal and human studies [11–13]. A long-term follow-up study of Caffeine therapy for apnea of prematurity (CAP) randomized control trial (RCT) showed that preterm neonates who received caffeine had a lower incidence of neurodevelopmental (ND) impairment defined as cerebral palsy (CP) or cognitive delay at 18–21 month corrected age (CA) [14]. Schmidt et al. [15] investigated this finding further and found that this ND advantage of caffeine was no longer present at 5 years of age or at 11 years of age, apart from being associated with a lower risk of motor impairment [16].

Despite the apparent increasing data on long-term ND outcomes surrounding caffeine therapy, there is a lack of evidence on the duration of its use in relation to ND outcomes. Investigations into the initiation of caffeine have been of recent interest, suggesting that prophylactic use may have benefits on certain outcomes [17–20]. Generally in infants ≤ 1250 g birth weight (BW), caffeine is initiated within the first 10 days of life and discontinued between 33 to 35 weeks postmenstrual age (PMA). This results in caffeine therapy duration spanning from less than 2 weeks to greater than 2 months depending on the gestational age (GA) at birth, in addition to other factors. To our knowledge, no other study has compared the ND outcomes of infants based on the duration of therapeutic caffeine use.

The objective of our study was to investigate if there is an association between duration of caffeine use and long-term ND outcomes at 3 years of age in preterm infants with BW ≤ 1250 g.

Material and methods

In this retrospective cohort study, all infants weighing ≤ 1250 g at birth admitted to the Foothills Medical Center NICU between January 2002 and December 2009 who received the first dose of caffeine within the first week of life and were followed up to 3 years CA in the regional neonatal follow-up clinic (NFC) were included in the study. The loading dose of caffeine base for management of AOP was 10 mg/kg. The maintenance dose was 2.5 mg/kg to 5 mg/kg every 24 h and usually commencing 24 h after the loading dose. Infants born with congenital abnormalities or chromosomal disorders or those who died were excluded. Criteria for commencing caffeine included: all premature infants born before 30 weeks' gestation, BW < 1500 g, receiving continuous positive airway pressure (CPAP) from birth, before extubation from the ventilator and for AOP. The usual criteria for stopping caffeine included: when infants reached 35 weeks' CA and or when infants were free from apnea requiring intervention for 7 days and apnea free for at least 5–7 days prior to discharge after discontinuing caffeine.

The study population was divided into three groups based on cessation of caffeine therapy after birth. Discontinuation of caffeine therapy was made at the discretion of the attending neonatologist. Early cessation of caffeine was defined if it was discontinued ≤ 14 days (ECC), intermediate cessation of caffeine 15–30 days (ICC) and late cessation of caffeine >30 days (LCC). Perinatal, neonatal and demographic data were compared among the three groups.

Perinatal and neonatal data were collected according to the Canadian Neonatal Network standards [21]. Postnatal steroids, specifically, dexamethasone was used in infants with BPD. There were no standard criteria for the use of postnatal steroids for BPD. This depended upon the discretion of the attending neonatologist with parental agreement to treat infants with severe BPD who had been ventilator dependent and had difficult to wean ventilator settings. In the NICU, attending neonatologists used either the high (0.89 mg/kg over 10 days) or low (0.65 mg/kg for 10 days) dose dexamethasone regimen for BPD.

ND assessments were carried out by the interdisciplinary team at the NFC, which included neonatologists, developmental pediatricians, psychologists, audiologists, a physiotherapist, an occupational therapist, and ophthalmologists. Parents provided informed consent for their children to be assessed. All ND outcomes were defined as outlined below, and these definitions remained constant throughout the study period. NICU clinical outcomes were collected retrospectively and NFC assessment findings were collected prospectively. Assessors were not blinded to infants' course in the NICU. Data were compiled by a trained data abstractor.

The primary outcome was the presence of ND impairment. ND impairment was considered to be present if any of the following were found: cerebral palsy (CP), borderline or severe cognitive delay, major (bilateral visual impairment) or minor visual impairment (corrected visual acuity <20/60 but >20/200 in the better eye), or hearing impairment or deafness. This retrospective cohort study was approved by the University of Calgary Conjoint Health Research Ethics Board.

Outcome definitions

Diagnosis of IVH was based on standards set by Papile et al. [22] using the worst cranial ultrasound results at any time during the patient's admission. Necrotizing enterocolitis (NEC) was classified based on Bell's staging (Bell stage > IIb). [23] RDS was defined by the need for mechanical ventilation >24 h, a supportive chest X-ray and/or treatment with surfactant [24]. BPD was defined as a requirement for supplemental oxygen and/or assisted ventilation at 36 weeks postmenstrual age (PMA) [24]. The International Classification of ROP was used to define the

diagnosis of ROP [25]. Late-onset sepsis was diagnosed if, after 3 days of life, any blood and/or cerebrospinal fluid cultures were positive for bacteria, viruses, or fungi.

CP was defined as a non-progressive disorder recognized primarily by impairment of movement, coordination, and posture. Findings of abnormal muscle tone and reflexes on the physical and neurological examination formed the basis for diagnosis [26]. CP was categorized as mild if it did not limit daily activities and functions, and moderate-severe if the child required appliances or assistance to perform daily activities and functions. Borderline cognitive function was defined as a full scale IQ score of 1–2 standard deviations (SD) below the mean, and cognitive delay as >2 SD below the mean, on the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) or Fourth Edition (WPPSI-IV). Visual impairment was defined as a corrected visual acuity <20/60 but >20/200 in the better eye, and blindness defined as bilateral blindness with corrected visual acuity <20/200 in the better eye. Deafness was defined as bilateral sensorineural hearing loss requiring amplification or cochlear implants. Hearing impairment was defined as sensorineural loss not requiring amplification or implants or unilateral loss requiring amplification.

Statistical analysis

Infant and maternal baseline characteristics were compared between the three groups using the Chi-square test for categorical variables and Kruskal–Wallis test for non-normally distributed continuous variables. Neonatal and 3-year neurodevelopmental outcomes were compared using the Chi-square or Fisher's exact test. Logistic regression was performed to explore the effect of caffeine duration on 3-year ND outcomes, after adjusting for clinically important neonatal variables. As our sample size limited the number of predictors we could include in a logistic regression model, we ran several models with caffeine duration, GA at birth, and maternal smoking as baseline variables, plus each of the neonatal risk factor separately, to explore whether the relationship between caffeine duration and ND impairment would change after accounting for known neonatal risk factors for ND impairment.

Results

Of the total 1055 live born infants ≤ 1250 g BW, 112 died before discharge from the NICU and six died after discharge from hospital prior to follow-up. Forty-four infants were excluded due to congenital anomalies, while 153 infants did not receive caffeine. Inclusion criteria were not met by an additional 232 infants as caffeine was not initiated in the first week of life. Sixty infants were excluded due to missing data on the duration of caffeine use. Of the 508 eligible infants, 448 (88.2%) completed 3-year CA follow-up visits at NFC. They were divided into ECC ($n = 139$), ICC ($n = 122$), and LCC ($n = 187$) groups (Fig. 1). The baseline characteristics of the three groups are outlined in Table 1.

Neonatal outcomes are listed in Table 2. RDS occurred in 82% of ICC infants compared to 92.5% in the LCC group ($p = 0.018$). The ICC group were also less likely to be diagnosed with BPD (37%) or ROP (5.3%) than both the ECC (BPD = 58.2%, ROP = 19.3%) and LCC groups (BPD = 49.1%, ROP = 9.1%). The ICC group had the shortest hospital stay with a median (IQR) number of days of 65 (21) ($p < 0.001$). Total days of ventilation and supplemental oxygen were the least in the ICC group with median (IQR) days of 8 (13) ($p = 0.001$) and 39 (125) ($p < 0.001$), respectively. The LCC cohort contained the least number of infants to receive postnatal dexamethasone (2.7%).

The duration of caffeine therapy did not impact the likelihood of ND impairment in children at 3 years CA (Fig. 2). When the groups were defined by the GA at which caffeine therapy was stopped, there was still no difference in ND impairment between the three groups (Table 3).

Logistic regression was used to adjust for GA, BPD, IVH, NEC, sepsis, ventilator days, postnatal dexamethasone use, blood transfusions, and maternal smoking. The adjusted odds ratios (95% CI) of ND impairment with length of caffeine usage and with PMA at time of caffeine stoppage are shown in Tables 4a and 4b, respectively.

Discussion

Our study revealed that the cessation of caffeine between 15–30 days after birth was associated with the least incidence of ND impairment in preterm infants ≤ 1250 g BW. Infants in the ICC group had a lower number of days on ventilation or supplemental oxygen. These infants were also less likely to be diagnosed with RDS, BPD, or ROP. Infants in the ICC group were also discharged home sooner. The LCC group did not show any difference in the ND parameters compared to either of the other two cohorts. Although caffeine has been shown to protect the developing brain [11–13], this study did not find any association between prolonged duration of caffeine (>30 days) and survival without impairment.

Caffeine has been shown to reduce the risk of severity of respiratory diseases including BPD and AOP. It has been shown to facilitate extubation with a shorter duration of intubation, decrease the need for treatment of PDA, reduce severity of ROP and improve motor function and visual perception in the later part of life in infants admitted to

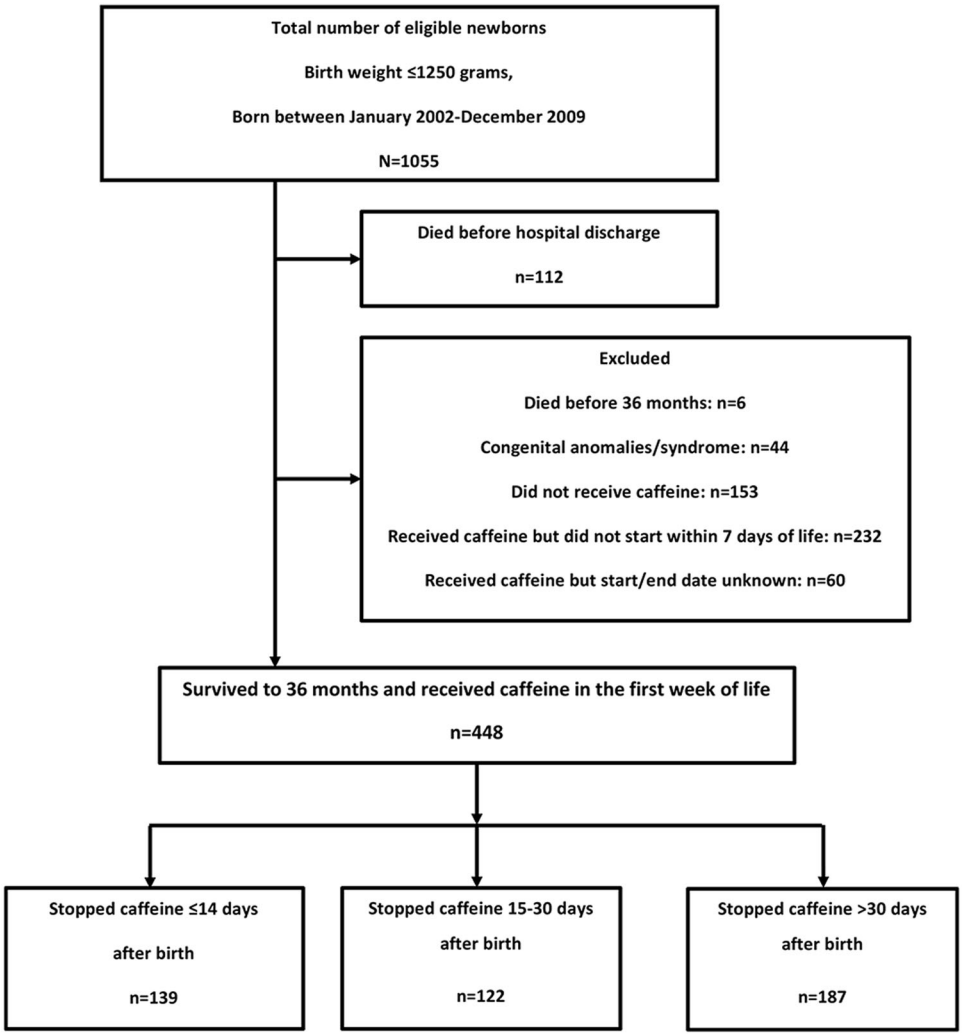

Fig. 1 Flow diagram of the study cohort

NICUs [3, 27, 28]. The reduced incidence of either RDS or BPD was only observed in the ICC group in our study. In the ICC group, infants' lungs are still very immature and have poor compliance. Caffeine acts as a bronchodilator, reduces diaphragmatic fatigue, and improves lung muscle function [3, 17]. Kassim et al. [29] measured specific lung function tests in eighteen infants who received caffeine and demonstrated an improvement in functional residual capacity, maximum pressures generated during occlusions at end inspiration and at end expiration. In the only other study to our knowledge that has looked at the length of caffeine therapy, Rhein et al. [30] suggested that intermittent hypoxia was reduced in infants whose caffeine use was extended to 40 weeks PMA compared to 34–37 weeks. This reduction in time spent with $SaO_2 < 90\%$ suggests an improvement in neural respiratory maturity/lung function. Our study focussed on the association of increased duration of caffeine during level III NICU admission with a median caffeine cessation at a GA of 33 weeks. Rhein et al.'s study extended caffeine use much beyond the neonatal time period and was focussed on the impact of caffeine after NICU discharge [30]. We did not find improvement in the outcomes of the LCC infants as would be suggested by Rhein et al.; however, the reduction of RDS, BPD and days of ventilation in our ICC infants is consistent with their findings.

Infants in the ECC group who were younger in GA, may have had underlying respiratory immaturity and/or poor compliance that led to a higher likelihood of developing BPD and increased days on mechanical ventilation. We speculate that those in the LCC group, may have had many apneic episodes and/or periodic breathing for a longer time, indicating a higher level of respiratory immaturity and so may have been more vulnerable to developing BPD. This also indicates that a late onset of respiratory distress or respiratory failure due to secondary surfactant deficiency or due to late onset sepsis may be associated with apnea. These conditions may also require late ventilation and may directly or indirectly contribute to development of BPD. BPD is a multifactorial disorder related to the size (BW,

Table 1 Baseline characteristics

Characteristic	ECC $n = 139$	ICC $n = 122$	LCC $n = 187$	p-value
Maternal				
Maternal education more than high school, *n* (%)	74/120 (61.7)	71/109 (65.1)	108/170 (63.5)	0.861
Blishen score, median (IQR)	43 (24) (missing = 18)	48 (26) (missing = 18)	49 (26) (missing = 16)	0.131
Maternal race aboriginal/first nations, *n* (%)	9/115 (7.8)	4/113 (3.5)	7/172 (4.1)	0.252
Maternal antihypertensive, *n* (%)	23/136 (16.9)	27/120 (22.5)	33/185 (17.8)	0.471
Smoking during pregnancy, *n* (%)	31/136 (30.2)	27/121 (22.3)	28 (15.0)	0.005
Antenatal corticosteroids, *n* (%)	123/135 (91.1)	110/121 (90.9)	170/186 (91.4)	0.989
Maternal antibiotics, *n* (%)	89/136 (65.4)	75/120 (62.5)	116/185 (62.7)	0.851
Chorioamnionitis, *n* (%)	20/129 (15.5)	22/117 (18.8)	42/181 (23.2)	0.234
Cesarean section, *n* (%)	84 (60.4)	78/121 (64.5)	110 (58.8)	0.608
Infants				
Birth weight-grams, median (IQR)	979 (339)	1010 (210)	980 (210)	0.524
Gestational age, week, median (IQR)	27 (3)	28 (2)	27 (2)	0.034
Gestational age at discharge-week, median (IQR)	37 (4) (missing = 6)	36 (3) (missing = 3)	38 (3) (missing = 5)	<0.001
Gestational age at caffeine stoppage, week, median (IQR)	28 (3)	31 (3)	33 (3)	<0.001
Male sex, *n* (%)	79 (56.8)	54 (44.3)	92 (49.2)	0.120
Singleton, *n* (%)	107 (77.0)	89 (73.0)	128 (68.5)	0.231
Inborn, *n* (%)	119 (85.6)	108 (88.5)	175 (93.6)	0.056
Small for gestational age (<10th %ile), n (%)	18 (13.0)	18 (14.8)	18/186 (9.7)	0.381
SNAP II score, median (IQR)	14 (10)	14 (11)	14 (10)	0.390

ECC early cessation of caffeine ≤ 14 days, *ICC* intermediate cessation of caffeine 15–30 days, *LCC* late cessation of caffeine >30 days, *IQR* inter quartile range, wk week

Table 2 Neonatal outcomes

Characteristic	ECC $n = 139$	ICC $n = 122$	LCC $n = 187$	p-value
Respiratory distress syndrome, *n* (%)	120 (86.3)	100 (82.0)	173 (92.5)	0.018
Supplemental oxygen at 36 weeks PMA, *n* (%)	71/122 (58.2)	34/92 (37.0)	81/165 (49.1)	0.009
Hospital stay-days, median (IQR)	77 (41) (missing = 6)	65 (21) (missing = 3)	74 (23) (missing = 5)	<0.001
Total ventilation/CPAP, days, median (IQR)	13 (39) (missing = 6)	8 (13) (missing = 1)	18 (25) (missing = 6)	0.001
Total suppl. oxygen-days, median (IQR)	109 (221) (missing = 28)	39 (125) (missing = 36)	57 (90) (missing = 40)	<0.001
Postnatal dexamethasone, *n* (%)	18 (13.0)	7/120 (5.8)	5/186 (2.7)	0.001
Diuretics (furosemide), *n* (%)	77/138 (55.8)	53/120 (44.2)	100/186 (53.8)	0.137
Retinopathy of prematurity stage ≥ III or laser treatment, *n* (%)	23/119 (19.3)	5/94 (5.3)	13/143 (9.1)	0.003
Necrotizing enterocolitis, *n* (%)	10 (7.2)	11 (9.0)	16/186 (8.6)	0.849
Intraventricular hemorrhage grade III or IV, *n* (%)	4/138 (2.9)	4 (3.3)	2/185 (1.1)	0.367
PVL, n (%)	2/137 (1.5)	5 (4.1)	1/186 (0.5)	0.055
Confirmed sepsis, *n* (%)	16 (11.5)	14 (11.5)	24/186 (12.9)	0.903
Patent ductus arteriosus, *n* (%)	71/137 (51.8)	55 (45.1)	99/186 (53.2)	0.353
Total blood transfusions-times, median (IQR)	1 (4) (missing = 1)	0 (1) (missing = 2)	1 (2) (missing = 8)	<0.001

CPAP continuous positive airway pressure, *ECC* early cessation of caffeine ≤ 14 days, *ICC* intermediate cessation of caffeine 15–30 days, *IQR* inter quartile range,

LCC late cessation of caffeine >30 days, *PMA* postmenstrual age, *PVL* periventricular leukomalacia

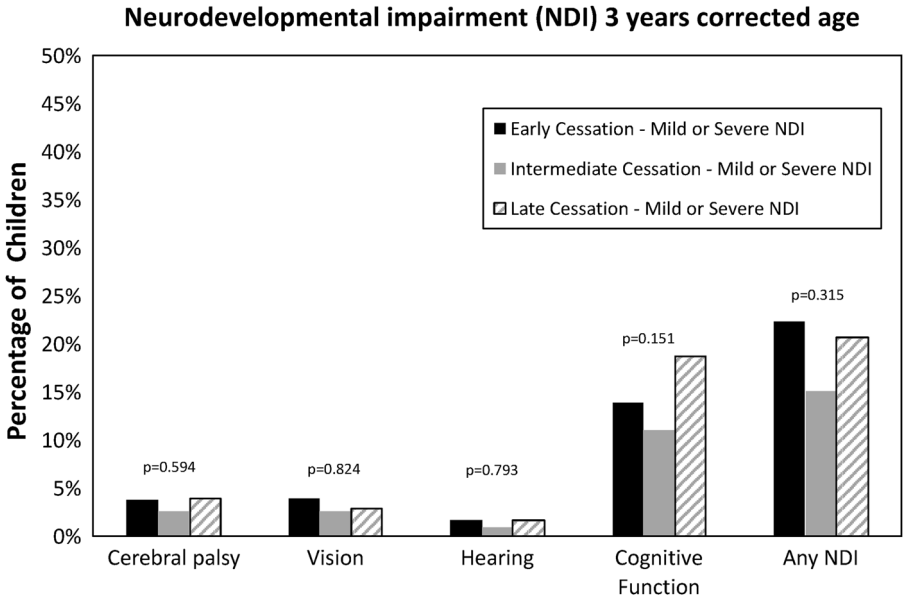

Fig. 2 Neurodevelopmental outcomes at 3 years corrected age

Table 3 Neurodevelopmental outcomes at 3 years CA based on the GA at which caffeine was stopped [n/N (%)]

Disabilities	Stopped caffeine <30 weeks GA $n = 144$	Stopped caffeine at 30–32 weeks GA $n = 148$	Stopped caffeine ≥ 33 weeks GA $n = 156$	*p*-value
Cerebral palsy				0.940
None	133/138 (96.4%)	134/140 (95.7%)	145/149 (97.3%)	
Mild	2/138 (1.5%)	2/140 (1.4%)	2/149 (1.3%)	
Moderate-severe	3/38 (2.2%)	4/140 (2.9%)	2/149 (1.3%)	
Blindness				0.827
None	134/137 (97.8%)	136/141 (96.5%)	143/148 (96.6%)	
Visual impairment	2/137 (2.2%)	5/141 (3.6%)	5/148 (3.4%)	
Legally blind	0/137 (0.0%)	0/141 (0.0%)	0/148 (0.0%)	
Deafness				0.480
None	132/134 (98.5%)	132/135 (97.8%)	146/147 (99.3%)	
Hearing impairment	1/134 (0.8%)	3/135 (2.2%)	1/147 (0.7%)	
Deaf	1/134 (0.8%)	0/135 (0.0%)	0/147 (0.0%)	
Cognitive function				0.169
Normal	114/130 (87.7%)	109/133 (82.0%)	118/139 (84.9%)	
Borderline	14/130 (10.8%)	17/133 (12.8%)	20/139 (14.4%)	
Delay	2/130 (1.5%)	7/133 (5.3%)	1/139 (0.7%)	
Any impairment				0.527
None	104/129 (80.6%)	100/130 (76.9%)	109/137 (79.6%)	
Mild	19/129 (14.7%)	22/130 (16.9%)	25/137 (18.3%)	
Severe	6/129 (4.7%)	8/130 (6.2%)	3/137 (2.2%)	

CA corrected age, *GA* gestational age

GA), immature lungs, ventilator induced trauma, PDA and its delayed closure, surfactant use, late onset of sepsis and hyperoxia [31]. In a retrospective analysis of 7509 infants admitted to Canadian NICU's between 2010 and 2011, late onset sepsis was shown to be associated with an increased risk for BPD thought to be due to the infection triggering an inflammatory response [32]. Between 25 to 36 weeks GA, during the phase of lung development, there is increased functional maturity of type II cells that secrete surfactant, maturity of alveolar ducts and thinning of the alveolar sacs

Table 4a Logistic regression models predicting mild to severe neurodevelopmental impairment based on caffeine use by postnatal days

Logistic regression models	Predictors	Adjusted odds ratio (95% confidence interval)
Length of caffeine usage + GA + smoking	ECC vs. LCC	0.892 (0.498–1.577)
	ICC vs. LCC	0.599 (0.314–1.143)
	ECC vs. ICC	1.489 (0.742–2.989)
	Gestational age at birth (weeks)	0.921 (0.795–1.066)
	Maternal smoking	1.041 (0.554–1.959)
Length of caffeine usage + GA + smoking + IVH Grade III/IV/PVL	ECC vs. LCC	0.841 (0.467–1.515)
	ICC vs. LCC	0.519 (0.266–1.015)
	ECC vs. ICC	1.620 (0.788–3.331)
	Gestational age at birth (weeks)	0.949 (0.817–1.103)
	Maternal smoking	0.960 (0.498–1.849)
	IVH Grade III/IV or PVL	6.856 (2.285–20.573)
Length of caffeine usage + GA + smoking + NEC	ECC vs. LCC	0.883 (0.497–1.571)
	ICC vs. LCC	0.606 (0.317–1.156)
	ECC vs. ICC	1.459 (0.725–2.936)
	Gestational age at birth (weeks)	0.909 (0.783–1.054)
	Maternal smoking	1.051 (0.558–1.978)
	NEC	0.527 (0.196–1.413)
Length of caffeine usage + GA + smoking + Sepsis	ECC vs. LCC	0.889 (0.500–1.581)
	ICC vs. LCC	0.602 (0.315–1.149)
	ECC vs. ICC	1.478 (0.735–2.970)
	Gestational age at birth (weeks)	0.910 (0.785–1.055)
	Maternal smoking	1.036 (0.550–1.950)
	Confirmed sepsis	0.614 (0.274–1.373)
Length of caffeine usage + GA + smoking + blood transfusions	ECC vs. LCC	0.858 (0.466–1.577)
	ICC vs. LCC	0.643 (0.335–1.235)
	ECC vs. ICC	1.334 (0.648–2.745)
	Gestational age at birth (weeks)	0.976 (0.827–1.150)
	Maternal smoking	0.950 (0.496–1.819)
	Number of blood transfusions	1.091 (0.961–1.238)
Length of caffeine usage + GA + smoking + oxygen at 36 weeks PMA	ECC vs. LCC	0.899 (0.481–1.679)
	ICC vs. LCC	0.648 (0.312–1.344)
	ECC vs. ICC	1.388 (0.627–3.073)
	Gestational age at birth (weeks)	0.928 (0.786–1.095)
	Maternal smoking	1.073 (0.544–2.114)
	Oxygen at 36 weeks PMA	0.979 (0.554–1.728)
Length of caffeine usage + GA + smoking + dexamethasone	ECC vs. LCC	0.840 (0.467–1.511)
	ICC vs. LCC	0.591 (0.308–1.131)
	ECC vs. ICC	1.423 (0.706–2.867)
	Gestational age at birth (weeks)	0.946 (0.813–1.102)
	Maternal smoking	1.001 (0.530–1.893)
	Postnatal dexamethasone	1.704 (0.700–4.149)
Length of caffeine usage + GA + smoking + SNAP II	ECC vs. LCC	0.941 (0.495–1.791)
	ICC vs. LCC	0.545 (0.262–1.076)
	ECC vs. ICC	1.727 (0.789–3.777)
	Gestational age at birth (weeks)	0.899 (0.763–1.059)

Table 4a (continued)

Logistic regression models	Predictors	Adjusted odds ratio (95% confidence interval)
Length of caffeine usage + GA + smoking + ventilation days	Maternal smoking	0.962 (0.485–1.908)
	SNAP II score	0.996 (0.966–1.027)
	ECC vs. LCC	0.884 (0.488–1.599)
	ICC vs. LCC	0.606 (0.315–1.163)
	ECC vs. ICC	1.459 (0.710–3.001)
	Gestational age at birth (weeks)	0.924 (0.775–1.102)
	Maternal smoking	1.015 (0.527–1.954)
	Ventilation/CPAP days	1.001 (0.986–1.016)

GA gestational age, *IVH* intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *PMA* postmenstrual age, *PVL* periventricular leukomalacia

for improved gas exchange. During this time period other secondary morbidities such as late onset of sepsis, multiple episodes of hypoxia and other factors that produce inflammatory mediators contribute to pulmonary inflammation before normal development of lungs is completed [33, 34]. A consequence of mechanical ventilation-associated lung injury is inflammation within the airways and the developing alveoli [34, 35]. This process further contributes to the development of BPD [34] and may have lessened the impact of caffeine on the neonatal lungs.

In Schmidt et al.'s CAP study [14], the participants from both the caffeine and placebo group were followed and completed ND assessments at 18–21 months, 5 years, and 11 years of age. This study did not evaluate the effects of duration of caffeine and cumulative doses of caffeine on ND outcomes. The 2 year follow-up showed a reduction in CP and cognitive delay [14]. This benefit disappeared at the 5 years follow-up [15] and only presented in the 11 years follow-up with a reduced risk of motor impairment [16]. Secondary analysis of the CAP study 5 years follow-up data by Favrais et al. [36] suggested reduced motor impairment was also present in the 5 year old children. Our study did not find any improvement in ND outcomes at 3 years follow-up in the late cessation group. A clinical trial examining caffeine dosing, but not duration, on neonatal outcomes found a similar lack of difference in outcomes between dosing groups at 12 months CA [37]. Caffeine has been shown to increase the cerebral cortical activity within 2 h of administration [38] and to increase the aEEG score at 36 weeks PMA [39]. Although both these studies suggest an improvement in brain function after caffeine administration, no long-term follow-up was done on these infants so it is difficult to make comparisons.

The ICC and LCC infants were also less likely to develop ROP. It can be speculated that this was related to the decreased respiratory support and, therefore, the exposure to supplemental oxygen and oxygen free radicals. Schmidt et al. indicated significant reductions in severe ROP (requiring treatment), in infants that received caffeine. Three studies looking at the use of early caffeine reported conflicting results, with only one indicating ROP was reduced in infants who received caffeine [6, 17, 18]. A potential explanation for the conflicting results could be the lack of control for duration of therapy as our study has demonstrated that duration of caffeine is associated with a decreased incidence of ROP.

Logistic regression was used to adjust for clinically important neonatal variables of GA, BPD, IVH, NEC, sepsis, ventilator days, Score for Neonatal Acute Physiology-II (SNAP II) scores, postnatal dexamethasone, blood transfusions, and maternal smoking on the ND outcomes of infants in each group. IVH, grade III and greater, was shown to be significantly associated with mild to severe ND impairment of our infants (Tables 4a and 4b), which is consistent with previous studies [40–43]. BPD is a multifactorial disease and related with duration of mechanical ventilation and postnatal use of steroids. However, these factors are also independently associated with poor neurodevelopmental outcome other than BPD. Therefore, we chose to include variables such as BPD, ventilator days, and postnatal dexamethasone to explore whether there was an effect of caffeine usage independent of known risk factors for NDI. We agree that many of these variables may be multicollinear. Therefore, we revised our logistic regression analysis by running several models, which included the baseline variables (caffeine duration, GA, and maternal smoking) plus each of the neonatal risk factors separately, to see whether the relationship between caffeine duration would change when these other risk factors were accounted for.

The strengths of our study include being the first to examine the impact of caffeine duration on ND impairment. The sample size was large and had an exceptional follow-up rate of 88%. The NFC is a regional clinic and serves Albertans from all areas of southern Alberta. The limitations

Table 4b Logistic regression models predicting mild to severe neurodevelopmental impairment with PMA at caffeine stoppage

Logistic regression models	Predictors	Adjusted odds ratio (95% confidence interval)
PMA at caffeine stoppage + GA + smoking	Stopped <30 weeks vs. ≥ 33 weeks PMA	0.706 (0.363–1.375)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	1.159 (0.645–2.084)
	Stopped <30 weeks vs. 30–32 weeks PMA	0.609 (0.318–1.167)
	Gestational age at birth (weeks)	0.868 (0.740–1.018)
	Maternal smoking	1.074 (0.574–2.007)
PMA at caffeine stoppage + GA + smoking + IVH Grade III/IV/PVL	Stopped < 30 weeks vs. ≥ 33 weeks PMA	0.622 (0.310–1.245)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	1.189 (0.657–2.151)
	Stopped < 30 weeks vs. 30–32 weeks PMA	0.523 (0.265–1.031)
	Gestational age at birth (weeks)	0.880 (0.747–1.035)
	Maternal smoking	1.000 (0.523–1.910)
	IVH Grade III/IV or PVL	6.935 (2.312–20.802)
PMA at caffeine stoppage + GA + smoking + NEC	Stopped < 30 weeks vs. ≥ 33 weeks PMA	0.713 (0.366–1.390)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	1.177 (0.654–2.120)
	Stopped < 30 weeks vs. 30–32 weeks PMA	0.606 (0.315–1.163)
	Gestational age at birth (weeks)	0.856 (0.728–1.006)
	Maternal smoking	1.079 (0.577–2.019)
	NEC	0.513 (0.191–1.379)
PMA at caffeine stoppage + GA + smoking + Sepsis	Stopped < 30 weeks vs. ≥ 33 weeks PMA	0.697 (0.357 –1.358)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	1.145 (0.636–2.063)
	Stopped < 30 weeks vs. 30–32 weeks PMA	0.608 (0.317–1.166)
	Gestational age at birth (weeks)	0.858 (0.730–1.007)
	Maternal smoking	1.073 (0.573–2.008)
	Confirmed sepsis	0.606 (0.271–1.354)
PMA at caffeine stoppage + GA + smoking + blood transfusions	Stopped < 30 weeks vs. ≥ 33 weeks PMA	0.678 (0.335–1.370)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	1.226 (0.670–2.243)
	Stopped < 30 weeks vs. 30–32 weeks PMA	0.553 (0.277–1.105)
	Gestational age at birth (weeks)	0.931 (0.783–1.108)
	Maternal smoking	0.966 (0.506–1.842)
	Number of blood transfusions	1.123 (0.990–1.274)
PMA at caffeine stoppage + GA + smoking + oxygen at 36 weeks PMA	Stopped < 30 weeks vs. ≥ 33 weeks PMA	0.769 (0.375–1.576)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	1.169 (0.605–2.258)
	Stopped < 30 weeks vs. 30–32 weeks PMA	0.658 (0.311–1.390)
	Gestational age at birth (weeks)	0.895 (0.750–1.067)
	Maternal smoking	1.109 (0.566–2.172)
	Oxygen at 36 weeks PMA	1.082 (0.603–1.939)
PMA at caffeine stoppage + GA + smoking + dexamethasone	Stopped < 30 weeks vs. ≥ 33 weeks PMA	0.662 (0.336–1.308)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	1.133 (0.629–2.038)
	Stopped < 30 weeks vs. 30–32 weeks PMA	0.585 (0.302–1.134)
	Gestational age at birth (weeks)	0.889 (0.755–1.047)
	Maternal smoking	1.022 (0.543–1.923)
	Postnatal dexamethasone	1.763 (0.730–4.261)
PMA at caffeine stoppage + GA + smoking + SNAP II	Stopped < 30 weeks vs. ≥ 33 weeks PMA	0.738 (0.356–1.528)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	0.964 (0.510–1.823)
	Stopped < 30 weeks vs. 30–32 weeks PMA	0.765 (0.367–1.597)
	Gestational age at birth (weeks)	0.852 (0.712–1.019)

Table 4b (continued)

Logistic regression models	Predictors	Adjusted odds ratio (95% confidence interval)
PMA at caffeine stoppage + GA + smoking + ventilation days	Maternal smoking	1.002 (0.511–1.963)
	SNAP II score	0.996 (0.966–1.027)
	Stopped < 30 weeks vs. ≥ 33 weeks PMA	0.705 (0.357–1.393)
	Stopped 30–32 weeks vs. ≥ 33 weeks PMA	1.269 (0.693–2.326)
	Stopped < 30 weeks vs. 30–32 weeks PMA	0.556 (0.282–1.094)
	Gestational age at birth (weeks)	0.894 (0.743–1.075)
	Maternal smoking	1.025 (0.535–1.962)
	Ventilation/CPAP days	1.005 (0.990–1.021)

GA gestational age, *IVH* intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *PVL* periventricular leukomalacia, *PMA* postmenstrual age

include the retrospective collection of NICU data, which by design includes bias. We also had to exclude 60 infants due to missing information on their caffeine intake.

Conclusions

This study identified the intermediate duration of caffeine use from 15–30 days after birth was associated with maximal improved clinical outcomes in infants ≤1250 g BW. The duration of caffeine use in premature infants is not associated with adverse long-term ND outcomes at 3 years CA. It would be beneficial to develop a large scale prospective randomized control trial to further investigate different durations of caffeine therapy and the impact on clinical outcomes.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Alden ER, Mandelkorn T, Woodrum DE, Wennberg RP, Parks CR, Hodson WA. Morbidity and mortality of infants weighing less than 1,000 grams in an intensive care nursery. Pediatrics. 1972;50:40–9.
2. Bhatia J. Current options in the management of apnea of prematurity. Clin Pediatr (Phila). 2000;39:327–36.
3. Aranda JV, Beharry K, Valencia GB, Natarajan G, Davis J. Caffeine impact on neonatal morbidities. J Matern Fetal Neonatal Med. 2010;23:20–3. Suppl 3
4. Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin DK, Smith PB, et al. Medication use in the neonatal intensive care unit. Am J Perinatol. 2014;31:811–21.
5. Patel RM, Leong T, Carlton DP, Vyas-Read S. Early caffeine therapy and clinical outcomes in extremely preterm infants. J Perinatol. 2013;33:134–40.
6. Taha D, Kirkby S, Nawab U, Dysart KC, Genen L, Greenspan JS, et al. Early caffeine therapy for prevention of bronchopulmonary dysplasia in preterm infants. J Matern Fetal Neonatal Med. 2014;27:1698–702.
7. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354:2112–21.
8. Fredholm BB. Astra Award Lecture. Adenosine, adenosine receptors and the actions of caffeine. Pharmacol Toxicol. 1995;76:93–101.
9. Dunwiddie TV, Masino SA. The role and regulation of adenosine in the central nervous system. Annu Rev Neurosci. 2001;24:31–55.
10. Boutilier RG. Mechanisms of cell survival in hypoxia and hypothermia. J Exp Biol. 2001;204:3171–81. (Pt 18)
11. Endesfelder S, Zaak I, Weichelt U, Bührer C, Schmitz T. Caffeine protects neuronal cells against injury caused by hyperoxia in the immature brain. Free Radic Biol Med. 2014;67:221–34.
12. Endesfelder S, Weichelt U, Strauß E, Schlör A, Sifringer M, Scheuer T, et al. Neuroprotection by caffeine in hyperoxia-induced neonatal brain injury. Int J Mol Sci. 2017;18:1.
13. Doyle LW, Cheong J, Hunt RW, Lee KJ, Thompson DK, Davis PG, et al. Caffeine and brain development in very preterm infants. Ann Neurol. 2010;68:734–42.
14. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med. 2007;357:1893–902.
15. Schmidt B, Anderson PJ, Doyle LW, Dewey D, Grunau RE, Asztalos EV, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA. 2012;307:275–82.
16. Schmidt B, Roberts RS, Anderson PJ, Asztalos EV, Costantini L, Davis PG, et al. Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity: An 11-year follow-up of the CAP randomized clinical trial. JAMA Pediatr. 2017;171:564–72.
17. Lodha A, Seshia M, McMillan DD, Barrington K, Yang J, Lee SK, et al. Association of early caffeine administration and neonatal outcomes in very preterm neonates. JAMA Pediatr. 2015;169:33–8.
18. Dobson NR, Patel RM, Smith PB, Kuehn DR, Clark J, Vyas-Read S, et al. Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. J Pediatr. 2014;164:992–e993.
19. Davis PG, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, et al. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. J Pediatr. 2010;156:382–7.
20. Gupte AS, Gupta D, Ravichandran S, Ma MM, Chouthai NS. Effect of early caffeine on neurodevelopmental outcome of very low-birth weight newborns. J Matern Fetal Neonatal Med. 2016;29:1233–7.

21. Network CN. Canadian Neonatal Network Annual Report 2015. 2015. Abstractor's Manual-The Canadian Neonatal Network. http://www.canadianneonatalnetworkorg/Portal/LinkClickaspx?fileticket=U4anC. Published 2011
22. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92:529–34.
23. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187:1–7.
24. Lodha A, Zhu Q, Lee SK, Shah PS, Network CN. Neonatal outcomes of preterm infants in breech presentation according to mode of birth in Canadian NICUs. Postgrad Med J. 2011;87:175–9.
25. An international classification of retinopathy of prematurity. Pediatrics. 1984;74:127–33.
26. Russman BS, Gage JR. Cerebral palsy. Curr Probl Pediatr. 1989;19:65–111.
27. Dobson N, Hunt C. Use in neonates: Indications, pharmokinetics, clinical effects, outcomes. NeoReviews. 2013;14:e540.
28. Dobson NR, Patel RM. The role of caffeine in noninvasive respiratory support. Clin Perinatol. 2016;43:773–82.
29. Kassim Z, Greenough A, Rafferty GF. Effect of caffeine on respiratory muscle strength and lung function in prematurely born, ventilated infants. Eur J Pediatr. 2009;168:1491–5.
30. Rhein LM, Dobson NR, Darnall RA, Corwin MJ, Heeren TC, Poets CF, et al. Effects of caffeine on intermittent hypoxia in infants born prematurely: a randomized clinical trial. JAMA Pediatr. 2014;168:250–7.
31. Bhandari A, Bhandari V. Pathogenesis, pathology and pathophysiology of pulmonary sequelae of bronchopulmonary dysplasia in premature infants. Front Biosci. 2003;8:e370–80.
32. Shah J, Jefferies AL, Yoon EW, Lee SK, Shah PS, Network CN. Risk factors and outcomes of late-onset bacterial sepsis in preterm neonates born at 32 weeks' gestation. Am J Perinatol. 2015;32:675–82.
33. Reuter S, Moser C, Baack M. Respiratory distress in the newborn. Pediatr Rev. 2014;35:417–28. quiz 429
34. Balany J, Bhandari V. Understanding the impact of infection, inflammation, and their persistence in the pathogenesis of bronchopulmonary dysplasia. Front Med (Lausanne). 2015;2:90.
35. Merritt TA, Deming DD, Boynton BR. The 'new' bronchopulmonary dysplasia: challenges and commentary. Semin Fetal Neonatal Med. 2009;14:345–57.
36. Favrais G, Tourneux P, Lopez E, Durrmeyer X, Gascoin G, Ramful D, et al. Impact of common treatments given in the perinatal period on the developing brain. Neonatology. 2014;106:163–72.
37. Gray PH, Flenady VJ, Charles BG, Steer PA, Group CCS. Caffeine citrate for very preterm infants: Effects on development, temperament and behaviour. J Paediatr Child Health. 2011;47:167–72.
38. Supcun S, Kutz P, Pielemeier W, Roll C. Caffeine increases cerebral cortical activity in preterm infants. J Pediatr. 2010;156:490–1.
39. Hassanein SM, Gad GI, Ismail RI, Diab M. Effect of caffeine on preterm infants' cerebral cortical activity: an observational study. J Matern Fetal Neonatal Med. 2015;28:2090–5.
40. Patra K, Wilson-Costello D, Taylor HG, Mercuri-Minich N, Hack M. Grades I-II intraventricular hemorrhage in extremely low birth weight infants: effects on neurodevelopment. J Pediatr. 2006;149:169–73.
41. Futagi Y, Toribe Y, Ogawa K, Suzuki Y. Neurodevelopmental outcome in children with intraventricular hemorrhage. Pediatr Neurol. 2006;34:219–24.
42. Al-Mouqdad M, Al-Abdi S, Scott JN, Hurley A, Tang S, Creighton D, et al. A new IVH scoring system based on laterality enhances prediction of neurodevelopmental outcomes at 3 years age in premature infants. Am J Perinatol. 2017;34:44–50.
43. Sarkar S, Bhagat I, Dechert R, Schumacher RE, Donn SM. Severe intraventricular hemorrhage in preterm infants: comparison of risk factors and short-term neonatal morbidities between grade 3 and grade 4 intraventricular hemorrhage. Am J Perinatol. 2009;26:419–24.