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ORIGINAL ARTICLE

Early caffeine therapy and clinical outcomes in extremely preterm infants

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Objective: To determine if early caffeine (EC) therapy is associated with decreased bronchopulmonary dysplasia (BPD) or death, decreased treatment of patent ductus arteriosus (PDA), or shortened duration of ventilation.

Study Design: In a retrospective cohort of 140 neonates $\leqslant$1250 g at birth, infants receiving EC (initiation <3 days of life) were compared with those receiving late caffeine (LC, initiation $\geqslant$3 days of life) using logistic regression.

Result: Of infants receiving EC, 25% (21/83) died or developed BPD compared with 53% (30/57) of infants receiving LC (adjusted odds ratio (aOR) 0.26, 95% confidence interval (CI) 0.09 to 0.70; $P<0.01$). PDA required treatment in 10% of EC infants versus 36% of LC infants (aOR 0.28, 95%CI 0.10 to 0.73; $P=0.01$). Duration of mechanical ventilation was shorter in infants receiving EC (EC, 6 days; LC, 22 days; $P<0.01$).

Conclusion: Infants receiving EC therapy had improved neonatal outcomes. Further studies are needed to determine if caffeine prophylaxis should be recommended for preterm infants.
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Keywords: methylxanthine therapy; bronchopulmonary dysplasia; patent ductus arteriosus; neonatal outcomes

Introduction

Despite improvements in survival for very low birth weight infants over the past two decades, bronchopulmonary dysplasia (BPD) and patent ductus arteriosus (PDA) remain common morbidities affecting this vulnerable population.[1] Over 40% of very low birth weight infants develop BPD based on recent estimates[2] and BPD remains the most common chronic lung disease of infancy. Neonates with BPD are at high risk of long-term lung disease, adverse neurodevelopmental outcomes and readmission to the hospital in the first year of life.[3] Despite the significant morbidities associated with BPD, few safe and effective therapies are available to prevent the disease.[4,5] In addition to BPD, a persistent PDA is a common problem affecting approximately half of neonates <29 weeks gestation with over two-thirds receiving drug therapy for closure and approximately one-fourth requiring surgical closure.[2] The presence of a persistent PDA is associated with increased neonatal morbidity such as prolonged ventilation[6] and, although controversial, may also increase the risk of developing BPD.[7,8]

Given the adverse outcomes associated with BPD and PDA, therapies targeted at reducing or preventing these morbidities are of significant value. In the Caffeine for Apnea of Prematurity (CAP) trial, caffeine therapy or placebo was initiated during the first 10 days of life (DOL) in infants weighing 500 to 1250 g at birth.[9] Infants treated with caffeine had a decreased incidence of both BPD and PDA when compared with placebo. In addition, caffeine therapy reduced the duration of mechanical ventilation by approximately 1 week. Importantly, caffeine therapy also resulted in improved long-term neurodevelopmental outcomes.[10] A *post-hoc* analysis of the CAP trial suggested that the efficacy of caffeine may be dependent on the timing of initiation of study drug.[11] However, the trial only included infants who met inclusion criteria by DOL 10, potentially excluding a significant group of infants who did not meet clinical criteria for treatment.

Early caffeine (EC) therapy may carry additional benefit during a critical period of susceptibility to both lung and brain injury in the first few days of a premature infant's life. We compared infants $\leqslant$1250 g at birth who received caffeine early in their hospital course with those who were treated later to determine if the timing of caffeine therapy would impact common morbidities of prematurity. Our primary hypothesis was that extremely preterm infants who receive EC therapy (initiation before DOL 3) would have a decreased incidence of BPD or death, when compared with infants who were treated with caffeine later in their hospital course (initiation at or after DOL 3). As secondary outcomes, we evaluated if EC initiation would be associated with a reduction in the treatment of PDA and a decreased duration of endotracheal ventilation.

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Methods

Patient population

This retrospective cohort study was performed at a single, regional referral level III neonatal intensive care unit (Grady Memorial Hospital, Atlanta, GA, USA). Infants born between January 2008 and June 2010 were eligible for inclusion in the study if they met the following three criteria: (1) birth weight (BW) $\leqslant 1250$ g (2) treatment with caffeine citrate at any point during hospital course (3) admission to our unit within 24 h after birth. Exclusion criteria included lack of information regarding timing of caffeine therapy or permanent transfer to another center for continued care.

An electronic medical record database (NeoData, Isoprime Corporation, Lisle, IL, USA) was queried to generate a list of all patients meeting the inclusion criteria. Further data was obtained by individual chart review. Appropriate oversight and approval was obtained from the Emory University Institutional Review Board and Grady Memorial Hospital Research Oversight Committee.

Definitions

Outcomes were compared by the timing of initiation of caffeine therapy with 'early' defined as initiation before DOL 3 and 'late' defined as initiation at or after DOL 3. We selected DOL 3 as the cutoff to divide the two groups, *a priori*, based on the median day of caffeine initiation in the CAP trial. The day of caffeine initiation was determined by the DOL at which the patient received the first dose of caffeine therapy, with the day of birth considered DOL 0. Caffeine therapy was initiated at the discretion of the attending neonatologist. BPD was defined as the requirement of any supplemental oxygen at a postmenstrual age (PMA) of 36 weeks or on the last day of hospitalization for infants discharged before 36 weeks PMA. In-hospital mortality was calculated for all patients who died before discharge. Pharmacologic treatment for PDA was determined by the need for either indomethacin or ibuprofen therapy for closure of a PDA after DOL 3. The cutoff using DOL 3 was performed to distinguish between those infants who received prophylactic indomethacin therapy from those who were treated for a persistent PDA. To account for infants with early mortality that precluded potential treatment of a PDA, neonates who died during the first 7 DOL were not included in the outcome analysis for PDA requiring treatment. The duration of endotracheal ventilation was determined for all infants who were ventilated at the initiation of caffeine therapy and the end of ventilation was defined as no endotracheal ventilation for at least 1 day. Gestational age (GA) was determined by the best obstetrical estimate using the date of the last menstrual period and/or dating ultrasound. The presence of intraventricular hemorrhage and periventricular leukomalacia were evaluated by routine ultrasound imaging interpreted by an attending pediatric radiologist. Retinopathy of prematurity was identified by routine screening. Infection was defined as a positive blood culture and treatment with antibiotics for at least 7 days. Medical necrotizing enterocolitis (NEC) was determined by a diagnosis of NEC made by an attending neonatologist. Surgical NEC was determined by the need for either exploratory laparotomy or peritoneal drain placement. Postnatal steroid use was defined as the receipt of either hydrocortisone or dexamethasone.

BPD estimator

To allow for a validated estimation of the baseline risk of moderate-to-severe BPD for patients in the study, a web-based BPD outcome estimator was utilized to estimate the probability of BPD using baseline and early clinical variables (available at https://neonatal.rti.org).[12] The BPD estimator was formulated using data from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) centers, of which Grady Memorial Hospital is a member. The estimator included the following clinical variables that were predictive of BPD or death: GA, BW, sex, race, ventilator type and fraction of inspired oxygen. First, estimated probabilities of moderate-to-severe BPD, using variables obtained on both postnatal days 1 and 3 to account for any early changes in postnatal predictor variables, were evaluated for individual patients in the cohort. Next, the mean-predicted probability of moderate-to-severe BPD was compared with observed rates of BPD for the entire cohort. Last, the mean-predicted probability of BPD was compared between neonates receiving early and late caffeine (LC) therapy to evaluate for any potential difference in the baseline risk of BPD.

Statistical analysis

PASW 18.0 for Windows (IBM, Armonk, NY, USA) was used for all statistical analyses. Median values with interquartile ranges were used for continuous variables, unless indicated otherwise. Statistical significance for unadjusted comparisons was performed using chi-square or Fisher's exact tests for categorical variables and Wilcoxon or Student's *t*-tests for continuous variables. For outcome analyses, logistic regression analysis with adjustment for covariates that are predictors of neonatal morbidity and mortality were included in separate models fit to the primary and secondary outcomes. For the outcome of death or BPD, the following covariates were entered into the model: BW, GA, sex, twin gestation, race, antenatal steroids (two doses), chorioamnionitis, surfactant therapy and outborn. Interaction between covariates was evaluated in the model and did not significantly affect the outcome. The following covariates were entered into the model and fit to the outcome of PDA requiring treatment: BW, GA, outborn and surfactant therapy. Our unit has set protocols for the use of prophylactic indomethacin therapy for the prevention of intraventricular hemorrhage in infants <1000 g at birth and prophylactic vitamin A therapy for the prevention of BPD in infants <1250 g at birth. As BW was included as a covariate in each of the models, further adjustment for the use of prophylactic vitamin A and indomethacin therapy was not performed. Covariates with a P-value of <0.10 or which improved

the predictability of the model were included in the final model for the outcome of death or BPD and PDA requiring treatment. Statistical significance was defined as a $P<0.05$.

Results

Over a 30-month period, 176 infants who weighed $\leqslant 1250$ g at birth were admitted to the Grady Memorial Hospital neonatal intensive care unit and 140 of these infants met the criteria for inclusion into the study. Although caffeine treatment was required for inclusion into this study, we gathered summary data for the infants who were $\leqslant 1250$ g at birth and did not meet criteria for inclusion. Of the 36 infants who were excluded, 14 (39%) died before hospital discharge and never received caffeine therapy. The median GA and BW for these infants were 24.5 weeks and 620 g, respectively. The remaining 22 infants who were excluded tended to be of relatively larger GA and BW (median GA 30.2 weeks and BW 1045 g). The majority of these infants did not meet inclusion criteria because they never received caffeine therapy, likely because they had little, if any, apnea. The remainder of these 22 infants were excluded because of permanent transfer to another center, which prevented evaluation of the primary outcome, or because they were admitted to our facility after 24 h of life. For the cohort of 140 infants who met inclusion and exclusion criteria, the median day of caffeine initiation was DOL 2 (interquartile range 1 to 5 days) and the mean day of caffeine initiation was DOL 5.3 (s.e.m. ± 0.81). For the entire cohort of 140 infants, the median GA was 27.0 weeks (interquartile range 25.5 to 28.1 weeks) and the median BW was 910 g (interquartile range 722 to 1069 g).

Early versus late caffeine groups

We divided the cohort into two groups based on timing of caffeine initiation. Of the 83 infants in the EC group, the median day of initiation was DOL 1 and 80% of infants received their initial dose of caffeine by DOL 1 (Table 1). For the 57 infants in the LC group, the median day of initiation was DOL 6 with a wide interquartile range (4 to 15.5 postnatal days). The median duration of caffeine therapy was similar between the EC and LC groups (EC: 40 days, LC: 39.5 days, $P=0.60$).

Patient characteristics

Although infants in the EC group were of slightly older GA (EC: 27.3 weeks, LC: 26.6 weeks, $P=0.03$), there was no significant difference in BW between infants in the EC and LC groups (EC: 940 g, LC: 910 g, $P=0.19$; Table 1). There were no significant differences in sex, race, twin gestation, antenatal steroid use, chorioamnionitis, or 1 and 5 min Apgar scores between groups. Infants in the LC group were more likely to be outborn (EC: 3.6%, LC: 17.5%, $P<0.01$), although this cohort only included outborn infants who were transferred to our center by 24 h of life. To account for these differences in baseline characteristics, both outborn and GA were included as covariates in our statistical models.

Table 1 Patient characteristics

Characteristics	*Early caffeine (<DOL 3)*	*Late caffeine (⩾DOL 3)*	P-*value*
Number of patients	83	57	
Initiation of caffeine therapy (DOL)			
Median	1	6	<0.01
Interquartile range	0–1	4–15.5	
Duration of caffeine therapy (days)			
Median	40	39.5	0.60
Interquartile range	21–58	28–61	
Gestational age (weeks)			
Median	27.3	26.6	0.03
Interquartile range	25.6–28.7	25.3–27.7	
Birth weight (g)			
Median	940	910	0.19
Interquartile range	730–1100	715–1035	
Sex			
Male	31 (37%)	27 (47%)	0.24
Female	52 (63%)	30 (53%)	
Race			
White	8 (10%)	5 (9%)	0.52
Black	59 (71%)	46 (81%)	
Hispanic	9 (11%)	4 (7%)	
Other	7 (8%)	2 (3%)	
Twin gestation	12 (15%)	6 (11%)	0.49
Antenatal steroids[a]	39 (47%)	27 (47%)	0.97
Chorioamnionitis	12 (15%)	7 (12%)	0.71
Apgar at 1 min (median)	4	4	0.66
Apgar at 5 min (median)	7	7	0.86
Outborn[b]	3 (4%)	10 (18%)	<0.01

Abbreviation: DOL, day of life.
[a]Only includes infants who received a complete course of antenatal steroids.
[b]Only includes outborn infants who were admitted by 24 h of life.
Data are presented as *n* (%) unless indicated otherwise.

Next, we evaluated neonatal morbidities and hospitalization characteristics between those infants who received early and late initiation of caffeine (Table 2). A similar proportion of infants in both groups required mechanical ventilation on DOL 0 and 1, and there was no significant difference in surfactant therapy between the groups. There were no significant differences in the rates of intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity or infection between groups. Additionally, there were no significant differences in the rates of intestinal perforation, NEC or postnatal steroid use between the groups.

Neonatal outcomes

Infants who received EC initiation had a significantly decreased incidence of the primary outcome of death or BPD when compared with those infants with later initiation (EC: 25.3%, LC: 52.6%, $P<0.01$) and this difference remained significant after adjustment for important predictors of BPD (adjusted odds ratio 0.26, 95% confidence interval 0.09 to 0.70; Table 3). This effect was accounted for by the decreased incidence of BPD in those infants treated with EC (EC: 23.6%, LC: 50.9%, $P=0.04$). In addition, infants receiving EC had lower levels of respiratory support at 36 weeks PMA (Supplementary Figure 1). In-hospital mortality did not differ significantly between groups (EC: 6.0%, LC: 5.3%, $P=0.64$).

Secondary outcomes included the presence of a PDA requiring treatment and the duration of endotracheal ventilation. Infants receiving EC had a significantly decreased need for pharmacologic or surgical treatment of a PDA when compared with infants receiving later therapy (EC: 10.4%, LC: 36.4%, $P=0.01$; Table 3). To evaluate the association between total median duration of endotracheal ventilation and timing of caffeine therapy, we evaluated the duration of endotracheal ventilation in infants who were ventilated at the initiation of caffeine therapy. The duration of endotracheal ventilation was significantly lower in infants receiving EC compared with LC (EC: 6 days, LC: 22 days, $P<0.01$). The median duration of ventilation after caffeine was initiated was similar between both groups (EC: 4 days, LC: 5 days).

To determine if the association between EC therapy and improved neonatal outcomes was specific to a particular subgroup of patients, BW-specific outcomes were evaluated (Table 4). Infants <750 g at birth who received EC had a lower incidence of BPD or death (EC: 52%, LC: 94%, $P<0.01$) while being closely matched in both GA (EC: 25.1 weeks, LC: 25.0 weeks, $P=0.54$) and BW (EC: 620 g, LC: 610 g, $P=0.80$). The frequency of PDA requiring treatment was significantly lower in infants with a BW between 750 and 999 g, and the duration of ventilation was significantly lower in each BW subgroup.

Finally, the BPD estimator was used to assess the probability of developing moderate-to-severe BPD using clinical characteristics from the first few days of life (postnatal day 1 and 3) to compare the baseline risk of BPD between groups (Table 5). For the entire

Table 2 Neonatal morbidities and hospital course

Variables	*Early caffeine (<DOL 3)*	*Late caffeine (≥DOL 3)*	P-*value*
Mechanical ventilation on DOL 0–1	59 (71%)	45 (79%)	0.30
Surfactant therapy	59 (72%)	48 (84%)	0.09
No IVH	46 (55%)	31 (54%)	0.90
Severe IVH (grade 3 or 4)	12 (14%)	8 (14%)	0.94
PVL	7 (8%)	4 (7%)	1.00
ROP >stage 1	20 (30%)	21 (41%)	0.20
ROP requiring laser surgery	2 (3%)	5 (10%)	0.24
Infection	16 (19%)	17 (30%)	0.15
Intestinal perforation	6 (7%)	3 (5%)	0.74
Medical NEC	8 (10%)	10 (18%)	0.15
Surgical NEC	1 (1%)	3 (5%)	0.30
Postnatal steroid use[a]	11 (13%)	12 (21%)	0.22

Abbreviations: DOL, days of life; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.
[a]Includes the use of both dexamethasone and hydrocortisone.
Data are presented as *n* (%).

Table 3 Neonatal outcomes by timing of caffeine initiation

Outcomes	*Early caffeine (<DOL 3)*	*Late caffeine (≥DOL 3)*	*Odds ratio (95% CI)*	*Adjusted odds ratio (95% CI)*	P-*value*
Primary outcome					
Death or BPD[a]	21 (25%)	30 (53%)	0.31 (0.15–0.63)	0.26 (0.09–0.70)	<0.01
Death	5 (6%)	3 (5%)	1.15 (0.26–5.03)	1.47 (0.30–7.26)	0.640
BPD[b]	17 (24%)	27 (51%)	0.30 (0.14–0.64)	0.33 (0.11–0.98)	0.04
Secondary outcomes					
PDA requiring treatment[c,d]	8 (10%)	20 (36%)	0.20 (0.08–0.51)	0.28 (0.10–0.73)	0.01
Pharmacologic only	7 (9%)	15 (27%)			
Surgical	1 (1%)	5 (9%)			
Duration of ventilation (median days)[e]	6	22			<0.01

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; DOL, days of life; PDA, patent ductus arteriosus.
[a]Outcome adjusted for gestational age, birthweight, sex, chorioamnionitis, surfactant therapy and antenatal steroid use.
[b]One infant died after developing BPD.
[c]Outcome adjusted for gestational age, birthweight and outborn.
[d]Eight infants were not included in the analysis (four died within 7 days of birth, four lacked details regarding PDA treatment).
[e]For infants ventilated at initiation of caffeine therapy.
Data are presented as *n* (%) unless indicated otherwise.

Table 4 Neonatal outcomes by timing of caffeine initiation and by birthweight subgroup

	Early caffeine (<DOL 3)	*Late caffeine (⩾DOL 3)*	P-*value*
Subgroup characteristics			
Gestational age, median (weeks)			
<750 g	25.1	25.0	0.54
750–999 g	26.9	26.1	0.16
1000–1250 g	28.7	27.7	<0.01
Birth weight, median (g)			
<750 g	620	610	0.80
750–999 g	860	879	0.58
1000–1250 g	1120	1073	0.06
Subgroup outcomes			
Death or BPD, n *(%)*[a]			
<750 g	11 (52)	17 (94)	<0.01
750–999 g	9 (31)	10 (53)	0.14
1000–1250 g	1 (3)	3 (15)	0.15
PDA requiring treatment, n *(%)*[b]			
<750 g	4 (22)	6 (35)	0.47
750–999 g	2 (8)	11 (61)	<0.001
1000–1250 g	2 (6)	3 (15)	0.35
Duration of ventilation, median (days)[c]			
<750 g	10	29	0.04
750–999 g	3	20	<0.01
1000–1250 g	2	7	<0.01

Abbreviations: BPD, bronchopulmonary dysplasia; DOL, days of life; PDA, patent ductus arteriosus.
[a]One infant died after developing BPD.
[b]Eight infants were not included in the analysis (four died within 7 days of birth, four lacked details regarding PDA treatment).
[c]For infants ventilated at initiation of caffeine therapy.

Table 5 Predicted probability of BPD

Predicted and observed risk of BPD	*All infants*	*Early caffeine (DOL <3)*	*Late caffeine (DOL ⩾3)*	P-*value*[a]
Probability of BPD on postnatal day 1 (mean)[b,c]	31%	29%	32%	0.32
Probability of BPD on postnatal day 3 (mean)[b,c]	31%	30%	33%	0.43
Observed incidence of BPD[d]	31%	24%	51%	<0.01

Abbreviations: BPD, bronchopulmonary dysplasia; DOL, days of life.
[a]Comparison of mean probability of BPD between early and late caffeine groups performed using Student's *t*-test.
[b]Prediction of BPD by postnatal age uses NIH definition and derived from web-based estimator (available at https://neonatal.rti.org).
[c]Of the 140 infants, 15 were not included. Four infants lacked data regarding fraction of inspired oxygen, 11 infants had variables outside of range for web-based calculator (9 with race/ethnicity outside of range and 2 with gestational age outside range).
[d]For observed incidence, BPD was defined as any oxygen requirement at 36 weeks postmenstrual age (study definition).

cohort, the mean-predicted probability of moderate-to-severe BPD was similar to the observed incidence of BPD, confirming the utility of the BPD estimator in this population of infants. Next, we assessed the probability of moderate-to-severe BPD in the EC and LC groups using baseline variables and predictor variables obtained on both postnatal days 1 and 3. The mean probability of developing moderate–to-severe BPD was similar between infants treated with EC and LC. In contrast, the observed incidence of BPD was significantly different between groups, suggesting that EC may potentially modify the risk of moderate-to-severe BPD.

Discussion

In this study, early initiation of caffeine therapy before DOL 3 in infants ⩽1250 g at birth was associated with decreased neonatal morbidity. Infants who received EC had approximately one-half the incidence of BPD or death when compared with infants undergoing later therapy. Importantly, this difference remained significant after adjusting for baseline differences between groups, including primary predictors of neonatal morbidity and mortality.[13] Additionally, infants <750 g who are considered to be at the highest risk for BPD or death, demonstrated the strongest association between EC initiation and decreased incidence of BPD or death. We utilized the BPD estimator to further characterize the baseline risk of BPD between both EC and LC groups. The results from the BPD estimator reassured us that infants who received EC therapy did not represent a group that had a lower baseline risk of BPD.

Given the limited number of therapies available for targeting the prevention of BPD, optimizing the use of a therapy that has been shown to be both safe and effective in reducing BPD may be an ideal strategy to decrease the burden of neonatal respiratory morbidity. Caffeine is a potential drug of choice for the prevention of BPD in very low birth weight infants.[4] In addition, caffeine is one of the most commonly used medications in the neonatal intensive care unit,[14] and it remains a highly cost-effective therapy.[15] Mechanistically, EC initiation may decrease pulmonary morbidity by improving pulmonary function and enhancing central respiratory drive. Caffeine therapy has been shown to improve lung function by improving minute ventilation,[16] pulmonary mechanics[17,18] and respiratory muscle contractility.[19] Additional potential benefits of methylxanthines include the protection of lung tissue against damage from injury.[20,21] Our findings suggest that early initiation during a period of critical susceptibility to injury may be necessary to confer the maximal benefit of caffeine therapy.

Interestingly, we found that EC initiation was associated with a decreased incidence of PDA requiring treatment. Potential mechanisms of action for this effect include diuresis and altered fluid balance,[22] increased cardiac output and blood pressure[23] or an improvement in overall pulmonary mechanics. Although caffeine may also affect several signaling molecules involved in ductal constriction, investigations on this effect are still inconclusive.[24–26] Possibly, improved respiratory morbidity in the neonate reduces the likelihood of a PDA requiring treatment, although the management of pharmacological and surgical ductal closure remains a controversial area of practice.[27]

The physiologic effects of caffeine may increase the success of early initial continuous positive airway pressure therapy or facilitate weaning from the ventilator and result in a reduction of endotracheal ventilation and protection against associated lung injury. These potential benefits of caffeine therapy are supported by findings in our study in which EC initiation was associated with an approximately 2 week decrease in the duration of endotracheal ventilation. Our findings are consistent with results from the CAP trial in which caffeine treatment resulted in approximately 1 week less of positive pressure ventilation.[9] In addition, a recent Cochrane analysis concluded that methylxanthine prophylaxis increases the chance of successful extubation within 1 week of treatment.[28] In our study, neonates successfully discontinued the use of endotracheal ventilation within 4 to 5 days following initiation of caffeine therapy, regardless of whether they received early or late caffeine initiation.

Although our study did not identify any potential adverse effects associated with the early initiation of caffeine therapy, the small sample size limited detection of clinically significant differences. Prior studies have raised concerns regarding the vasoconstrictive effects of caffeine therapy.[29] Potentially, these vasoconstrictive effects may be amplified by concomitant administration of prophylactic indomethacin therapy, which also has vasoconstrictive properties.[30] However, a large, multicenter randomized controlled trial did not identify any safety concerns related to the use of caffeine citrate.[9,10]

Limitations of this study include its design as a single-center, retrospective cohort study with a predominately African-American population. In addition, we were unable to ascertain the indication for caffeine therapy in each patient and no institutional protocol directed caffeine use. Although we did not evaluate long-term effects in our study, caffeine treatment has been shown to reduce the incidence of long-term neurologic impairment and cerebral palsy.[10] The role of caffeine in protection against neurodevelopmental impairment may be explained, in part, by its effect on improving respiratory morbidity. However, a recent investigation demonstrating improved white matter microstructural development in caffeine-treated infants suggests that other unidentified mechanisms of action are likely to play a role.[31] Although the retrospective study design prohibits the establishment of causality and differences in patient characteristics may have influenced the timing of caffeine initiation, we attempted to account for these differences in baseline characteristics through both adjustments in our statistical models and the use of subgroup analyses. However, we acknowledge our inability to control for all factors that are reflective of early severity of illness or that potentially influenced the clinical outcomes. Our findings of decreased BPD in infants receiving EC, although indicative of a substantial benefit for at-risk preterm infants, remain hypothesis-generating and necessitate additional investigation including validation in a large, multicenter cohort of patients.

In conclusion, our results demonstrate that EC initiation is associated with decreased BPD in extremely preterm infants. Given the limited number of safe and well-studied therapies that are effective in decreasing the burden of BPD,[4,5] caffeine remains a potential first-line therapy of choice for the prevention of BPD in preterm infants. Optimizing the timing of caffeine therapy by initiating earlier treatment or by instituting universal prophylaxis may carry additional benefits over its conventional use as a treatment for apnea of prematurity or for facilitation of extubation. Our data suggest that the treatment effect of EC use may be substantial compared with later initiation. However, randomized controlled trials of caffeine prophylaxis to prevent neonatal morbidities, such as BPD and PDA, are necessary to conclusively support the routine use of caffeine as a preventative therapy and to ensure the safety of early initiation of caffeine in extremely preterm infants.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)