Published in final edited form as:

J Pediatr. 2017 November ; 190: 108–111.e1. doi:10.1016/j.jpeds.2017.07.006.

Early Caffeine Prophylaxis and Risk of Failure of Initial Continuous Positive Airway Pressure in Very Low Birth Weight Infants

Ravi M. Patel, MD, MSc^{1,2}, Kanecia Zimmerman, MD, MPH³, David P. Carlton, MD^{1,2}, Reese Clark, MD⁴, Daniel K. Benjamin, PhD⁵, and P. Brian Smith, MD, MHS, MPH³

¹Emory University School of Medicine

²Children's Healthcare of Atlanta, Atlanta, GA

³Duke University, Durham, NC

⁴Pediatric Medical Group, Greenville

⁵Clemson University, Clemson, SC

Abstract

Objective—To test the hypothesis that early caffeine treatment on the day of birth, compared with later treatment in very low birth weight (VLBW, <1500 g) infants receiving continuous positive airway pressure (CPAP) therapy, is associated with a decreased risk of CPAP failure in the first week of life.

Study design—Multicenter, observational cohort study in 366 US neonatal intensive care units. We evaluated inborn, VLBW infants discharged from 2000 to 2014, who received only CPAP therapy without surfactant treatment on day of life (DOL) 0, had a 5-minute Apgar ≥ 3 , and received caffeine in first week of life. We used multivariable conditional logistic regression to compare the risk of CPAP failure, defined as invasive mechanical ventilation or surfactant therapy on DOL 1–6, by timing of caffeine treatment as either early (initiation on DOL 0) or routine (initiation on DOL 1–6).

Results—We identified 11 133 infants; 4528 (41%) received early caffeine and 6605 (59%) received routine caffeine. Median gestational age was lower in the early caffeine group, 29 weeks (25th, 75th percentiles; 28, 30) vs the routine caffeine group, 30 weeks (29, 31); $P < 0.001$. The incidence of CPAP failure on DOL 1–6 was similar between the early and routine caffeine groups: 22% vs 21%; adjusted OR = 1.05 (95% CI: 0.93, 1.18).

Conclusions—Early caffeine treatment on the day of birth was not associated with a decreased risk of CPAP failure in the first week of life for VLBW infants initially treated with CPAP.

Reprint requests: Ravi M. Patel, MD, MSc, Division of Neonatology, Emory University School of Medicine, 2015 Uppergate Dr NE, 3rd floor, Atlanta, GA 30322. rmpatel@emory.edu.

The other authors declare no conflicts of interest.

Portions of this study were presented at the Pediatric Academic Societies Annual Meeting, San Diego, California, April 25–28, 2015.

Continuous positive airway pressure (CPAP) is a widespread approach to support respiration after birth in very low birth weight (VLBW) infants and is often initiated in the delivery room. However, many infants receiving initial CPAP therapy develop CPAP failure, defined as the need for rescue therapy with surfactant or mechanical ventilation, with reported rates of 22% to 36% for VLBW infants.¹⁻³ Compared with infants who succeed with initial CPAP therapy, those who fail are at higher risk for adverse outcomes, including death or bronchopulmonary dysplasia (BPD).^{2,4} Therefore, strategies to reduce CPAP failure may improve outcomes for VLBW infants.

For some infants, pharmacologic therapies such as caffeine could potentially reduce the incidence of CPAP failure.⁵ Caffeine is widely used to treat or prevent apnea related to prematurity⁶ but likely also has beneficial effects on pulmonary compliance and airway resistance,^{7,8} minute ventilation,⁹ and respiratory muscle contractility¹⁰ that can lead to more effective respiration. Although initiation of caffeine within the first 2 days after birth has been associated with a lower risk of BPD in VLBW infants,¹¹⁻¹⁴ few studies have evaluated the effect of early caffeine on the risk of initial CPAP failure.

Our primary objective was to test the hypothesis that initiation of caffeine therapy on the day of birth, compared with later initiation, in VLBW infants receiving initial CPAP therapy, is associated with a decreased risk of CPAP failure. As secondary outcomes, we compared the days of CPAP support and maximal fraction of inspired oxygen (FiO₂) requirement >0.3 in the first week of life between infants receiving early and routine caffeine therapy.

Methods

We used data from the Pediatrix Medical Group Clinical Data Warehouse, which prospectively captures information from the electronic medical record of daily progress notes and other documentation of clinicians involved in the care of infants. Information is collected regarding maternal history and demographics, drugs, laboratory results, culture results, and diagnoses. Details of drug doses and dosing intervals were not recorded. This study was approved by the Duke University Institutional Review Board without the need for consent because the study data did not include patient identifiers. This dataset has been reported previously¹⁵

We included all infants <1500 g birth weight discharged from one of 366 neonatal intensive care units in the Pediatrix Medical Group between 2000 and 2014. We excluded infants who (1) were outborn; (2) died in the first week of life; (3) had a 5-minute Apgar <3; (4) had missing length of stay; (5) did not receive caffeine; (6) received invasive respiratory support on the day of birth; (7) received surfactant on the day of birth; or (8) had no respiratory support data on the day of birth.

We defined the day of birth as day of life (DOL) 0. We defined early caffeine therapy as initiation on DOL 0 and defined routine caffeine therapy as initiation on DOL 1-6. We defined CPAP failure, our primary composite outcome, as the receipt of invasive mechanical ventilation or surfactant therapy on DOL 1-6. We defined invasive mechanical ventilation as

the use of high-frequency or conventional endotracheal ventilation and defined surfactant therapy as treatment with calfactant, beractant, poractant, lucinactant, or colfosceril.

Secondary outcomes (duration of CPAP therapy and maximal $\text{FiO}_2 > 0.3$) were assessed on DOL 1-6. We also reported the following clinical outcomes between groups: in-hospital mortality, BPD, medical or surgical necrotizing enterocolitis, severe retinopathy of prematurity, ligation of a patent ductus arteriosus, and severe intraventricular hemorrhage (grade 3 or 4). As we reported these outcomes in a previous study¹¹ and did not consider differences in these outcomes as hypotheses to be tested in this study, we only reported event numbers and frequencies. We defined BPD as the need for respiratory support at a postmenstrual age of 36^{0/7}-36^{6/7} weeks if <32 weeks gestational age (GA) or at 28-34 postnatal days if ≥ 32 weeks GA.¹¹ We defined severe retinopathy of prematurity as infants who required treatment. We defined small for GA (SGA) as weight <10% for GA using published intrauterine growth curves.¹⁵ Race and ethnicity were based on the documentation in the medical record. Pressor therapy was treatment with one of the following medications: dobutamine, dopamine, epinephrine, norepinephrine, or milrinone.

Statistical Analyses

We used Stata v 14.2 for Windows (StataCorp, College Station, Texas) for all statistical analysis. We described continuous variables using median and 25th and 75th percentiles. We compared baseline characteristics between infants receiving early and routine caffeine using the Wilcoxon rank sum test. We analyzed the primary outcome using conditional logistic regression with adjustment for potential baseline confounding variables. We conditioned on center and adjusted for GA (categorical), birth weight (categorical), SGA, sex, race/ethnicity 5-minute Apgar score (categorical), receipt of antibiotic therapy on DOL 0-1, receipt of pressor therapy on DOL 0-1, and discharge year (categorical). We compared the secondary dichotomous outcome of maximal $\text{FiO}_2 > 0.3$ on DOL 1-6 between infants receiving early and routine caffeine using a model adjusting for the same covariates as the primary analysis. For days of CPAP on DOL 1-6, a continuous variable, we used multivariable fixed effects negative binomial regression to estimate the incidence rate ratio between early and routine caffeine groups. These models included adjustment for GA, birth weight, SGA, sex, race/ethnicity, 5-minute Apgar score, discharge year, and center (all specified as categorical variables). We also performed exploratory post-hoc subgroup analysis using interaction terms in our multivariable regression model to assess heterogeneity between early caffeine and CPAP failure among 2 stratified subgroups: infants with birth weight <1000 g vs ≥ 1000 g and GA <28 vs ≥ 28 weeks. These models included adjustment for the same covariates in the primary multivariable model with the exception of the stratifying variable.

Results

Of the 151 209 VLBW infants in the dataset from 2000 to 2014, 11 133 (7%) infants met the inclusion criteria and were evaluated for the study outcomes (Figure 1).

Among the study cohort, 79% weighed 1000-1499 g at birth, 49% were of white race, and the median 5-minute Apgar score was 8 (25th, 75th percentiles: 8,9). A total of 4528 (41%) infants received early caffeine and 6605 (59%) received routine caffeine (Table I). GA was

lower in the early caffeine group, compared with the routine caffeine group (median weeks [25th, 75th percentiles]: 29 [28, 30] vs 30 [29, 31]; $P < .001$).

The early initiation of caffeine was relatively infrequent in 2000, with 21% of infants receiving therapy on the day of birth (Figure 2). From 2001 to 2007, the frequency of early caffeine use in a given year ranged from 16% to 22%. In 2008, 28% of infants received early caffeine and in 2014 67% received early caffeine.

Overall, 21% of infants had CPAP failure on DOL 1-6, with 15% receiving subsequent invasive mechanical ventilation, 14% receiving treatment with surfactant, and 8% receiving both surfactant and invasive mechanical ventilation (Table II). We found no difference in the risk of CPAP failure between infants receiving early caffeine and routine caffeine (22% vs 21%). The age at CPAP failure was similar in both groups (median DOL [25th, 75th percentiles]: 1 [1-2]). Infants receiving early caffeine had no difference in exposure to a maximal $\text{FiO}_2 > 0.3$ in the first week of life compared with those receiving routine caffeine (27% vs 32%). Infants receiving early caffeine had no difference in duration of CPAP therapy (median [25th, 75th percentiles]: 3 [1, 6] vs 2 [1, 4] days). Overall, adverse clinical outcomes were low, with in-hospital mortality after 1 week of age and BPD occurring in 1% and 12% of infants, respectively (Table III). In subgroup analysis, we detected no heterogeneity in the association between early caffeine and CPAP failure among infants with a birth weight < 1000 g vs ≥ 1000 g and GA < 28 vs ≥ 28 weeks (Table IV).

Discussion

We report that early caffeine therapy, compared with routine caffeine, is not associated with a decreased risk of CPAP failure among VLBW infants receiving initial CPAP therapy. This study evaluated the relationship between caffeine therapy initiated on the day of birth and subsequent CPAP failure in the first week of life. Several prior studies have demonstrated an association between initiation of caffeine in the first few days of life, compared with later initiation, and a reduced risk of BPD^{11-13,16} and shorter duration of respiratory support with ventilation or CPAP therapy.^{11,12,14} The lack of a beneficial effect of caffeine on CPAP failure in this study suggests the mechanisms that influence CPAP failure may be different from those influencing the risk of BPD or duration of respiratory support and may not be altered by the physiologic effects of caffeine on respiratory mechanics and apnea.

Overall, 21% of infants developed CPAP failure after the day of birth. By comparison, CPAP failure occurred in 24% of infants < 1250 g in a previous report.³ Studies among less mature infants 25-28 weeks of gestation have reported CPAP failure rates of 43% in the first 72 hours after birth, more than twice the 21% incidence among more mature infants born at 29-32 weeks of gestation.⁴ The slightly lower incidence of CPAP failure identified in our study compared with prior studies may be attributable to our study design, which excluded infants who developed CPAP failure on the day of birth.

Our study was not designed to evaluate the effect of caffeine initiated in the delivery room or within a few hours of birth on CPAP failure on the day of birth. In a recent pilot trial, infants < 29 weeks' GA were randomized to early prophylactic use of caffeine before 2 hours of age

or caffeine initiation at 12 hours of age.¹⁷ The study reported that fewer infants in the early caffeine treatment arm required intubation by 12 hours of age, compared with those receiving caffeine at 12 hours of age, although this was not a statistically significant difference (27% vs 70%, $P = .08$). By contrast, there was no reduction in days of mechanical ventilation between infants receiving caffeine before 2 hours vs 12 hours of age (mean 6 vs 3 days; $P = .40$). Another recent study of 30 infants born at 24–30 weeks' GA demonstrated that caffeine treatment initiated in the delivery room, compared with later initiation in the neonatal intensive care unit, resulted in increases in respiratory effort measured by minute volumes and tidal volumes but no significant difference in respiratory rate at 7–9 minutes after birth.¹⁸

Beginning in 2008, we noted an increase in the proportion of VLBW infants who were treated with caffeine therapy on the day of birth with two-thirds of infants receiving early caffeine in 2014. Although the factors driving this increase were not evaluated in this study, the increase in use of early caffeine followed the publication of the short- and long-term outcomes in 2006 and 2007, respectively, from the Caffeine for Apnea of Prematurity Trial, a multicenter, randomized trial evaluating caffeine use in extremely preterm infants.^{19,20}

Our study has several strengths. Our large sample size allowed us to provide estimates of association with good precision and ensured that we would be able to detect clinically important differences in the risk of CPAP failure between groups. We were able to identify a sample of infants who received exclusive CPAP therapy on the day of birth who could potentially derive benefit from prophylactic use of caffeine as an approach to decrease CPAP failure. In addition, we were able to adjust for multiple potential baseline confounders, including measures of illness severity and center.

We acknowledge the limitations of this study. The observational design prevents any definitive causal determination of the effects of early caffeine prophylaxis on CPAP failure. We could not adjust for all factors that were associated with the decision by the clinician to start caffeine on the day of birth and were associated with CPAP failure. Therefore, residual confounding of our results is possible. We could not evaluate the effect of heterogeneity in timing of initiation of caffeine on the day of birth (eg, within a few hours of birth or after 12 hours of age) on our study outcomes. In addition, our selection criteria were designed to analyze a relatively homogenous group of VLBW infants with lower illness acuity, by excluding infants needing surfactant on the day of birth or those with a low Apgar score. Therefore, the effects of early caffeine among all VLBW infants, including those receiving surfactant but not mechanical ventilation, on subsequent CPAP failure requires additional study.

Acknowledgments

Supported by the National Institutes of Health (NIH). R.M.P. received salary support from the NIH National Center for Advancing Translational Sciences (NCATS) (UL1TR000454 and KL2TR000455) and the National Heart, Lung, and Blood Institute (K23HL128942). K.Z. receives funding from the Duke Clinical and Translational Science Awards (KL2TR001115). P.B.S. receives research support from the NIH (NIH-1R21HD080606-01), NCATS (UL1TR001117), the National Institute of Child Health and Human Development (NICHD) (HHSN275201000003I), and the Food and Drug Administration (1R18-FD005292-01); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp).

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Glossary

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
DOL	Day of life
FiO₂	Fraction of inspired oxygen
GA	Gestational age
SGA	Small for GA
VLBW	Very low birth weight

Figure 1.
Flow diagram of subject selection and outcome evaluation.

Figure 2.
Receipt of early caffeine prophylaxis by year among study infants.

Table I
Baseline infant characteristics

	Early caffeine	Routine caffeine
	4528 N (%)	n = 6605 N (%)
GA in wk, median [25 th , 75 th percentile]	29 [28, 30]	30 [29, 31]
Birthweight by group		
<1000g	1282/4528 (28%)	1089/6605 (16%)
1000-1499 g	3246/4528 (72%)	5516/6605 (84%)
Female	2372/4524 (52%)	3431/6602 (52%)
Race/ethnicity		
White	2044/4377 (47%)	3400/6370 (53%)
Black	1280/4377 (29%)	1480/6370 (23%)
Hispanic	779/4377 (18%)	1065/6370 (17%)
Other	274/4377 (6%)	425/6370 (7%)
Apgar score at 5 min, median [25 th , 75 th percentile] *	8 [8, 9]	8 [8, 9]
Antibiotics on DOL 0 or 1	3301/4528 (73%)	4603/6605 (70%)
Pressor therapy on DOL 0 or 1	334/4528 (7%)	418/6605 (6%)

DOL, day of life.

* Infants with Apgar score <3 were excluded from study.

Table II

Study outcomes

	Early caffeine	Routine caffeine	aOR* or IRR [‡]
	N = 4528	N = 6605	(95% CI)
Primary outcome evaluated during the first postnatal wk			
CPAP failure ^{*,†}	990 (22%)	1376 (21%)	1.05 (0.93,1.18)
Invasive ventilation	683 (15%)	1029 (16%)	1.06 (0.92,1.21)
Surfactant therapy	662 (15%)	919 (14%)	1.00 (0.88,1.15)
Secondary outcomes evaluated during the first postnatal wk			
Maximal FiO ₂ >0.3 [*]	1209 (27%)	2119 (32%)	1.05 (0.94,1.17)
Days of CPAP [‡]	3 [1, 6]	2 [1,4]	1.02 (0.99,1.05)

IRR, incidence rate ratio.

* aORs compare early caffeine with routine caffeine. Models include adjustment for GA, birthweight, SGA, sex, race/ethnicity, 5-minute Apgar, antibiotics (DOL 0 or 1), pressor therapy (DOL 0 or 1), discharge year, and center.

[†] 632 (5.6%) subjects not analyzed in regression model because of missing data or because some small sites did not have enough data.

[‡] Continuous outcome, reported as median [25th, 75th percentile]. Model estimates are IRR comparing early caffeine to routine caffeine. Model includes adjustment for GA, birthweight, SGA, sex, race/ethnicity, 5-minute Apgar, discharge year and center.

Table III
Descriptive clinical outcomes

	Early caffeine	Routine caffeine
	N = 4528	N = 6605
Mortality	64/4327 (1%)	73/6334 (1%)
BPD	569/4345 (13%)	686/6323 (11%)
Necrotizing enterocolitis	244/4528 (5%)	316/6605 (5%)
Severe retinopathy of prematurity	37/4528 (0.8%)	28/6605 (0.4%)
Ligation of patent ductus arteriosus	50/4528 (1%)	64/6605 (1%)
Severe intraventricular hemorrhage	62/4528 (1%)	88/6605 (1%)

Table IV
Primary study outcome by subgroups

	Early caffeine N = 4528	Routine caffeine N = 6605	Stratified aOR* (95% CI)
Primary outcome evaluated during the first postnatal wk			
CPAP failure by GA subgroups [†]			
<28wk	290/963 (30%)	220/716 (31%)	0.87 (0.65,1.17)
28wk	700/3565 (20%)	1156/5889 (20%)	1.13 (1.00,1.29)
CPAP failure by birth weight subgroups [‡]			
<1000 g	367/1282 (29%)	318/1089 (29%)	0.91 (0.72,1.16)
1000 g	623/3246 (19%)	1058/5516 (19%)	1.13 (0.99,1.29)

* aORs compare early caffeine with routine caffeine.

[†] Models include adjustment for birthweight, SGA, sex, race/ethnicity, 5-minute Apgar, antibiotics (DOL 0 or 1), pressor therapy (DOL 0 or 1), discharge year, and center. No significant subgroup heterogeneity was observed (interaction $P = .89$).

[‡] Models include adjustment for GA, SGA, sex, race/ethnicity, 5-minute Apgar, antibiotics (DOL 0 or 1), pressor therapy (DOL 0 or 1), discharge year, and center. No significant subgroup heterogeneity was observed (interaction $P = .25$).