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

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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 the 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. *(J Pediatr 2017;190:108-11).*

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 prematurity[6] but likely also has beneficial effects on pulmonary compliance and airway resistance,[7,8] minute ventilation,[9] and respiratory muscle contractility[10] 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 (FiO_2) 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

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
DOL	Day of life
FiO_2	Fraction of inspired oxygen
GA	Gestational age
SGA	Small for GA
VLBW	Very low birth weight

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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 previously.[15]

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 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 study[11] 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 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**; available at www.jpeds.com).

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**; available at www.jpeds.com). 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.

Table I. Baseline infant characteristics

	Early caffeine n = 4528 N (%)	Routine caffeine n = 6605 N (%)
GA in wk, median [25th, 75th percentile]	29 [28, 30]	30 [29, 31]
Birthweight by group		
<1000 g	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 [25th, 75th 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.