Trends in Caffeine Use and Association between Clinical Outcomes and Timing of Therapy in Very Low Birth Weight Infants

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Objective To examine the effect of early initiation of caffeine therapy on neonatal outcomes and characterize the use of caffeine therapy in very low birth weight (VLBW) infants.

Study design We analyzed a cohort of 62 056 VLBW infants discharged between 1997 and 2010 who received caffeine therapy. We compared outcomes in infants receiving early caffeine therapy (initial dose before 3 days of life) and those receiving late caffeine therapy (initial dose at or after 3 days of life) through propensity scoring using baseline and early clinical variables. The primary outcome was the association between the timing of caffeine initiation and the incidence of bronchopulmonary dysplasia (BPD) or death.

Results We propensity score–matched 29 070 VLBW infants at a 1:1. Of infants receiving early caffeine therapy, 3681 (27.6%) died or developed BPD, compared with 4591 infants (34.0%) receiving late caffeine therapy (OR, 0.74; 99% CI, 0.69-0.80). Infants receiving early caffeine had a lower incidence of BPD (23.1% vs 30.7%; OR, 0.68; 95% CI, 0.63-0.73) and a higher incidence of death (4.5% vs 3.7%; OR, 1.23; 95% CI, 1.05-1.43). Infants receiving early caffeine therapy had less treatment of patent ductus arteriosus (OR, 0.60; 95% CI, 0.55-0.65) and a shorter duration of mechanical ventilation (mean difference, 6 days; $P < .001$).

Conclusion Early caffeine initiation is associated with a decreased incidence of BPD. Randomized trials are needed to determine the efficacy and safety of early caffeine prophylaxis in VLBW infants. *(J Pediatr 2014;164:992-8)*.

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Caffeine is one of the most commonly prescribed medications in preterm infants.[1] In the Caffeine for Apnea of Prematurity (CAP) trial published in 2006, infants allocated to receive caffeine had a lower incidence of bronchopulmonary dysplasia (BPD) compared with control infants.[2] In early follow-up at age 18-21 months, improved neurodevelopmental outcomes, including a lower incidence of cerebral palsy, were noted in infants allocated to receive caffeine, but these benefits were not as dramatic at age 5 years.[3,4]

Approximately one-half of the early neurodevelopmental improvement of caffeine therapy was explained by improved respiratory morbidity, including an approximate 1-week reduction in the duration of mechanical ventilation (MV).[2] Caffeine may decrease pulmonary morbidity through its beneficial effects on respiratory mechanics,[5-8] and possibly by protecting lung tissue against damage from injury.[9-11] Given the demonstrable benefits of caffeine, understanding its current clinical use is of significant value.

Several aspects of caffeine therapy remain unknown. For example, a post hoc analysis of the CAP trial suggests that early caffeine therapy (ie, initiation before day of life [DOL] 3) is associated with decreased use of endotracheal intubation and positive pressure ventilation when compared with late caffeine therapy (ie, initiation at or after DOL 3).[12] The risks and benefits of early caffeine therapy compared with late caffeine therapy and the routine use of caffeine prophylaxis have not been yet evaluated in a randomized, controlled trial. In our recent investigation of the association of timing of caffeine therapy and clinical outcomes in a single-center, retrospective study, infants with early initiation of caffeine therapy demonstrated decreased risk of BPD and patent ductus arteriosus (PDA).[13] In

BPD	Bronchopulmonary dysplasia	IVH	Intraventricular hemorrhage
CAP	Caffeine for Apnea of Prematurity	MV	Mechanical ventilation
CPAP	Continuous positive airway pressure	NEC	Necrotizing enterocolitis
DOL	Day of life	PDA	Patent ductus arteriosus
GA	Gestational age	PS	Propensity score
FiO_2	Fraction of inspired oxygen	ROP	Retinopathy of prematurity
HFOV	High-frequency oscillatory ventilation	VLBW	Very low birth weight

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addition, trends in the use of caffeine citrate, approved by the Food and Drug Administration in 1999,[14] have yet to be studied in a large population of very low birth weight (VLBW) infants. Caffeine has several advantages over other methylxanthines, including a long half-life and a wide therapeutic window that does not require therapeutic drug monitoring.[15]

We compared the effects of early and late caffeine therapy on short-term neonatal outcomes, including death and BPD, among others, in a large group of US neonatal intensive care units. We also characterized the use of methylxanthines from 1997 to 2010. We hypothesize that: (1) early caffeine initiation is associated with improved neonatal outcomes; (2) centers have shifted to earlier initiation of caffeine therapy; and (3) caffeine has replaced the use of aminophylline and theophylline in the current era.

Methods

We used a large, multicenter dataset from the Pediatrix Medical Group.[16] The use of this dataset has been described previously.[1] Infants discharged between 1997 and 2010 were eligible for evaluation of primary and secondary outcomes if they met the following inclusion criteria: (1) receipt of caffeine during the course of hospitalization; (2) VLBW (<1500 g birth weight); and (3) admission within 1 day of birth. Exclusion criteria included treatment with multiple methylxanthines and early mortality (death on DOL 0-3). In addition, we examined all VLBW infants discharged between 1997 and 2010, including infants not treated with caffeine or treated with other methylxanthines (theophylline and aminophylline), to characterize trends in the use of methylxanthines. This study was approved by the Duke University Medical Center Institutional Review Board.

Postnatal age was based on DOL, with the day of birth defined as DOL 0. We compared patient characteristics and outcomes by timing of initiation of caffeine therapy, with early defined as initiation before DOL 3 and late defined at initiation on or after DOL 3. We determined the type of respiratory support provided for all infants and the duration of respiratory support for infants requiring MV. Our primary outcome measure was the association between timing of initiation of caffeine therapy and incidence of BPD or death. We calculated mortality for all infants who died before hospital discharge. We defined BPD as the need for any respiratory support at postmenstrual age 36 0/7-36 6/7 weeks if <32 weeks gestational age (GA) at birth or at 28-34 postnatal days if ≥32 weeks GA at birth. Infants discharged before the BPD evaluation period on room air were defined as having no BPD, and those receiving respiratory support before the evaluation period were defined as missing for BPD status.

To account for the competing outcomes of mortality and BPD, we used a composite outcome measure of BPD or death. Secondary outcomes were prespecified and selected based on clinical outcomes that potentially could be affected by caffeine therapy based on results from our previous study[13] and the CAP trial.[2] We defined treatment of a PDA as the receipt of either indomethacin or ibuprofen therapy for closure of a PDA after DOL 3 or surgical ligation. We defined late-onset sepsis as a positive blood culture on or after DOL 3. We defined necrotizing enterocolitis (NEC) as the diagnosis of medical or surgical NEC. Additional neonatal comorbidities were identified by the diagnosis of the corresponding morbidity in the patient's medical record.

To reduce bias and confounding related to treatment with early caffeine, we used propensity score (PS) matching to obtain similar matched populations of infants receiving early and late caffeine therapy. Matching was chosen over other PS methods, such as stratifying on the quintiles, for ease of interpretation and because greater residual imbalance tends to be eliminated by matching.[17] For the PS model, we used baseline demographic and early clinical variables that could predict early caffeine treatment and/or were predictors of our primary outcome.[18] The following baseline variables were used in the PS model: GA, birth weight, sex, race, small for GA status, Apgar score at 5 minutes, receipt of antenatal steroids, outborn, center, and birth year. In addition, the following early clinical variables were used: apnea on DOL 0 or 1, level of respiratory support on DOL 1, maximal fraction of inspired oxygen (FiO_2) on DOL 1, and the use of high-frequency oscillatory ventilation (HFOV) on DOL 1. A greedy match algorithm was used to match infants receiving early and late caffeine therapy.[19] Patients were matched without replacement down to a 1-digit match, and any patients who could not be matched beyond this level were excluded.

For unmatched patients, the Wald χ^2 test with adjustment for clustering by center was used for categorical variables, and the Student t test or Wilcoxon rank-sum test was used for continuous variables. For PS-matched patients, the McNemar test for categorical variables was used for binary categorical variables, the Bhakpar generalized McNemar test was used for multiple categorical variables, and the paired t test or Wilcoxon rank-sum test was used for continuous variables. Trends in the use of methylxanthines over time were evaluated using the Spearman rank correlation coefficient. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). A P value <.01 was considered significant.

Results

Of the 54 707 infants meeting the study's inclusion criteria, 29 070 (53%) were PS-matched at 1:1 (**Figure 1**). PS-matched infants in the early and late caffeine groups had similar baseline characteristics, with no significant differences in any of the matched variables, including mean birth weight (1055 g vs 1054 g; P = .77) and GA (28.1 weeks vs 28.0 weeks; P = .70) (**Table I**).

Early Respiratory Characteristics

After matching, statistically significant, but minimal differences were seen between infants receiving early and