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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)*.

See editorial, p 957

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

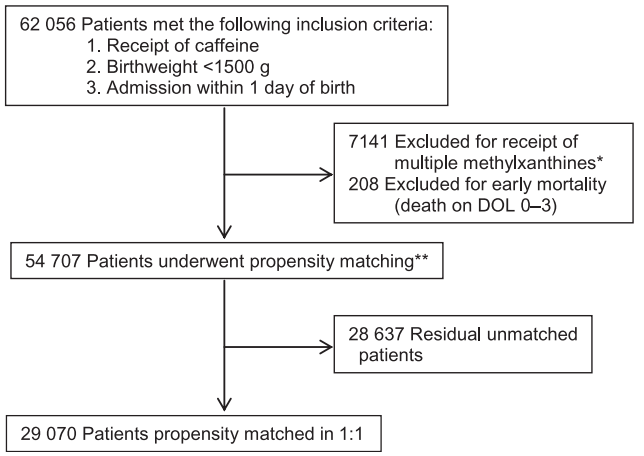

Figure 1. After PS matching, 29 070 patients (53%) meeting the inclusion criteria were eligible for analysis of primary and secondary outcomes. *Patients receiving multiple methylxanthines included in the evaluation of trends in methylxanthine use over time. **Select comparisons of the full cohort meeting inclusion and exclusion criteria, including unmatched patients.

late caffeine therapy in the rates of continuous positive airway pressure (CPAP) therapy (22.4% vs 21.6%), conventional ventilation (49.7% vs 51.4%), and HFOV (11.9% vs 10.9%) on DOL 1 ($P = .002$). The mean maximal FiO_2 on DOL 1 was similar in the 2 groups (0.27 vs 0.27; $P = .74$) (**Table I**).

Infants in the early caffeine therapy group were more likely to receive higher levels of respiratory support, including MV and HFOV, at the initiation of caffeine therapy (**Table II**; available at www.jpeds.com).

Clinical Characteristics

There was no difference in the incidence of NEC ($P = .50$) between the PS-matched groups (**Table III**). The incidence of central nervous system complications, including any intraventricular hemorrhage (IVH) ($P < .001$), severe (grade 3 or 4) IVH ($P < .001$), and periventricular leukomalacia ($P = .001$), was lower in the early caffeine group, as was the incidence of retinopathy of prematurity (ROP) ($P < .001$) and of ROP requiring treatment ($P < .001$). The early caffeine group also demonstrated a lower incidence of pulmonary interstitial emphysema ($P < .001$), although this complication was uncommon in both groups.

In the early caffeine group, the mean age at initiation of therapy was DOL 1 (**Table III**), with the majority of infants starting treatment within a day after birth (**Figure 2**; available at www.jpeds.com). In comparison, the late caffeine group had a wide range of age at initiation, with the mean of DOL 11. Surfactant use was similar in the 2 groups ($P = .17$). In addition, the rate of prophylactic indomethacin use was lower in the early caffeine group ($P < .001$).

Primary Outcome

For the primary outcome of BPD or death, the early caffeine group had a lower odds of BPD or death (OR, 0.74; 99% CI,

Table I. Baseline and early clinical characteristics

Characteristics	All patients			PS-matched patients*		
	Early caffeine (n = 30 891)	Late caffeine (n = 23 816)	*P* value	Early caffeine (n = 14 535)	Late caffeine (n = 14 535)	*P* value
Birth weight, g, mean (5th, 95th percentile)	1076 (650, 1450)	1009 (560, 1450)	<.0001	1055 (630, 1447)	1054 (590, 1460)	.77
GA, wk, mean (5th, 95th percentile)	28.2 (25.0, 32.0)	27.7 (24.0, 32.0)	<.0001	28.1 (25.0, 31.0)	28.0 (24.0, 32.0)	.70
Sex, male, n (%)	15 538 (50.3)	12 267 (51.5)	.01	7386 (50.8)	7395 (50.9)	.92
Race, n (%)†						
White	15 051 (50.3)	11 648 (50.6)	.88	7467 (51.4)	7511 (51.7)	.88
Black	7531 (25.2)	5620 (24.4)		3579 (24.6)	3592 (24.7)	
Hispanic	5783 (19.3)	4507 (19.6)		2707 (18.6)	2655 (18.3)	
Other	1580 (5.3)	1252 (5.4)		782 (5.4)	777 (5.4)	
Multiple gestation, n (%)	8423 (27.3)	6605 (27.7)	.33	4017 (27.6)	4036 (27.8)	.80
Small for GA, n (%)	2852 (9.2)	2265 (9.5)	.42	1383 (9.5)	1343 (9.2)	.42
Apgar at 1 min, median (IQR)	6 (4-8)	6 (4-7)	<.0001	6 (4-7)	6 (4-7)	.29
Apgar at 5 min, median (IQR)	8 (7-9)	8 (7-9)	<.0001	8 (7-9)	8 (7-9)	.93
Any antenatal steroids, n (%)	24 562 (79.5)	18 123 (76.1)	<.0001	11 427 (78.6)	11 475 (79.0)	.49
Outborn, n (%)‡	3473 (11.3)	3236 (13.8)	<.0001	1602 (11.0)	1613 (11.1)	.84
Respiratory support on DOL 1, n (%)§						
Room air	1936 (6.4)	1804 (7.7)	<.0001	1242 (8.5)	1255 (8.6)	.002
Hood oxygen	135 (0.5)	102 (0.4)		56 (0.4)	78 (0.5)	
Nasal cannula	1048 (3.5)	643 (2.8)		482 (3.3)	440 (3.0)	
High-flow nasal cannula	1707 (5.7)	750 (3.2)		544 (3.7)	572 (3.9)	
CPAP	9177 (30.4)	3675 (15.8)		3249 (22.4)	3145 (21.6)	
MV	13 966 (46.2)	10 830 (46.7)		7230 (49.7)	7465 (51.4)	
HFOV	2238 (7.4)	5401 (23.3)		1732 (11.9)	1580 (10.9)	
Maximal FiO_2 on DOL 1, mean (5th, 95th percentile)	0.26 (0.21, 0.41)	0.30 (0.21, 0.60)	<.0001	0.27 (0.21, 0.50)	0.27 (0.21, 0.45)	.74
Apnea on DOL 0 or 1, n (%)	8045 (26)	1095 (4.6)	<.0001	859 (5.9)	817 (5.6)	.16

*Patients PS-matched on all baseline characteristics and early respiratory support variables (except Apgar at 1 min), as well as birth year and center.
†A total of 1735 (3.2%) patients with missing data.
‡A total of 514 (0.9%) patients with missing data.
§A total of 1295 (2.4%) patients with missing data.

Table III. Clinical characteristics

Characteristics	All patients: Early caffeine (n = 30 891)	All patients: Late caffeine (n = 23 816)	All patients: *P* value	PS-matched patients: Early caffeine (n = 14 535)	PS-matched patients: Late caffeine (n = 14 535)	PS-matched patients: *P* value
Comorbidities, n (%)						
Early-onset sepsis*	378 (1.3)	455 (2.1)	<.001	183 (1.4)	256 (2.0)	<.001
Pulmonary interstitial emphysema	428 (1.4)	1148 (4.8)	<.001	233 (1.6)	468 (3.2)	<.001
IVH	8320 (26.9)	8629 (36.2)	<.001	4267 (29.4)	4745 (32.7)	<.001
Severe IVH†	1406 (4.6)	2401 (10.1)	<.001	755 (5.2)	1103 (7.6)	<.001
Periventricular leukomalacia	422 (1.4)	579 (2.4)	<.001	228 (1.6)	301 (2.1)	.001
NEC‡	2488 (8.1)	1980 (8.3)	.49	1219 (8.4)	1187 (8.2)	.50
ROP	9273 (30.0)	9881 (41.5)	<.001	4515 (31.1)	5266 (36.2)	<.001
Therapy for ROP	745 (2.4)	1650 (6.9)	<.001	404 (2.8)	727 (5.0)	<.001
Therapies						
Age at caffeine initiation, d						
Mean (5th,95th percentile)	1 (0,2)	13 (3,45)	-§	1 (0,2)	11 (3,37)	-§
Median (IQR)	1 (0-1)	7 (4-16)		1 (1-2)	6 (4-12)	
Duration of caffeine therapy, d						
Mean (5th,95th percentile)	37 (5,72)	33 (5,68)	<.001	37 (4,72)	32 (5,67)	<.001
Median (IQR)	36 (23-49)	30 (17-45)		36 (22-50)	29 (17-43)	
Surfactant use, n (%)	19 856 (64.3)	16 342 (68.6)	.002	9649 (66.4)	9539 (65.6)	.17
Prophylactic vitamin A, n (%)	2501 (8.1)	1462 (6.1)	.03	1038 (7.1)	774 (5.3)	<.001
Prophylactic indomethacin, n (%)¶	4103 (13.3)	4752 (20.0)	<.001	2115 (14.6)	2744 (18.9)	<.001
Pressor therapy, n (%)‖	5671 (18.4)	9030 (37.9)	<.001	3136 (21.6)	4599 (31.6)	<.001

*Early-onset sepsis defined as a positive blood culture before DOL 3. A total of 4755 (8.7%) unmatched patients and 2843 (9.8%) PS-matched patients had missing data.
†IVH grade III or IV.
‡Medical or surgical NEC.
§Statistical comparison not performed as groups separated by age at caffeine initiation.
¶Prophylactic indomethacin defined as initiation of indomethacin before DOL 3.
‖Includes the use of any of the following cardiac agents: dobutamine, dopamine, epinephrine, norepinephrine, or milrinone.

0.69-0.80) and a lower odds of BPD in survivors (OR, 0.68; 95% CI, 0.63-0.73) (Table IV). The difference in risk of BPD between the early and late caffeine groups was 16.1% before PS matching and 7.6% in matched infants. The early caffeine group received less respiratory support at 36 weeks postmenstrual age (Table II). The odds of death were higher in the early caffeine group (OR, 1.23; 95% CI, 1.05-1.43), with a risk difference of 0.8% between the 2 groups (Table IV).

To determine whether the outcomes were specific to infants of a particular GA, we performed a subgroup analysis by GA strata. In this subgroup analysis, early caffeine therapy was associated with a consistent effect on the odds of BPD in infants of all GA subgroups (Table V; available at www.jpeds.com). Infants at <24 weeks GA who received early caffeine therapy had an increased odds of death, which was not seen in any of the other GA strata.

Secondary Outcomes

PDA requiring treatment was less frequent in the early caffeine group (OR, 0.60; 95% CI, 0.55-0.65) (Table IV). Mean weight

Table IV. Clinical outcomes

Outcomes	All patients: Early caffeine (n = 30 891)	All patients: Late caffeine (n = 23 816)	All patients: *P* value	PS-matched patients*: Early caffeine (n = 14 535)	PS-matched patients*: Late caffeine (n = 14 535)	PS-matched patients*: OR (99% CI)	PS-matched patients*: *P* value
Primary outcomes, n (%)							
BPD or death	6898 (24.3)	8855 (40.2)	<.001	3681 (27.6)	4591 (34.0)	0.74 (0.69-0.80)	<.001
BPD in survivors†	5823 (20.6)	8068 (36.7)	<.001	3070 (23.1)	4154 (30.7)	0.68 (0.63-0.73)	<.001
Death	1172 (3.8)	998 (4.2)	.08	659 (4.5)	542 (3.7)	1.23 (1.05-1.43)	<.001
Secondary outcomes, n (%)							
Treatment of PDA	2753 (8.9)	4655 (19.6)	<.001	1794 (12.3)	2765 (19.0)	0.60 (0.55-0.65)	<.001
Late-onset sepsis‡	6021 (21.1)	6361 (29.8)	<.001	3083 (21.2)	3559 (24.5)	0.81 (0.76-0.88)	<.001
Duration of MV, d							
Mean (5th-95th percentile)	10 (0, 46)	21 (0, 73)	<.001	11 (0, 48)	17 (0, 64)		<.001
Median (IQR)	2 (0-9)	9 (1-34)		3 (1-12)	6 (0-25)		
Weight gain, g/d, mean (5th,95th percentile)§							
DOL 7	−6.3 (−24.4, 12.7)	−3.3 (−23.4, 17.1)	<.001	−6.3 (−25.1, 12.9)	−3.5 (−23.6, 17.0)		<.001
DOL 14	5.8 (−5.0, 17.5)	6.1 (−5.4, 18.6)	.011	5.6 (−5.1, 17.1)	6.5 (−5.0, 18.9)		<.001
DOL 28	13.9 (5.0, 24.1)	13.0 (3.6, 23.9)	<.001	13.6 (4.8, 23.6)	13.7 (4.3, 24.4)		.40

*Early and late caffeine groups were PS matched on the following baseline variables: GA, birth weight, sex, race, multiple gestation, small for GA, Apgar score at 5 min, any antenatal steroids, outborn, center, and birth year. In addition, the following early clinical variables on DOL 1 were used: apnea, type of respiratory support, maximal FiO_2, and need for HFOV.
†A total of 2195 (4.0%) unmatched infants and 1031 (3.5%) PS-matched infants (early, 558; late, 473) had missing data for BPD.
‡A total of 4755 (8.7%) unmatched infants and 2843 (9.8%) PS-matched infants (early, 1379; late, 1464) had missing data for late-onset sepsis.
§Mean daily weight gain (or loss) from birth to DOL listed.

loss was greater during the first week of life (DOL 7) in the early caffeine group (early, −6.3 g/day; late, −3.5 g/day; $P < .001$); however, the difference in mean weight gain between the groups was no longer present by DOL 28 (early, 13.6 g/day; late, 13.7 g/day; $P = .40$). Infants in the early caffeine group experienced fewer days on MV (mean difference, 6 days; $P < .001$). The odds of late-onset sepsis were also lower in the early caffeine group (OR, 0.81; 95% CI, 0.76-0.88).

Trends in Caffeine Use

The use of caffeine demonstrated a shift toward earlier initiation over time (**Figure 3**; available at www.jpeds.com). The age at caffeine initiation decreased from a mean of DOL 10 (5th, 95th percentile, 0, 46) and a median of DOL 4 (IQR 2-10) in 1997 to a mean of DOL 4 (5th, 95th percentile, 0, 18) and median of DOL 1 (IQR, 0-3) in 2010. In addition, caffeine progressively replaced aminophylline and theophylline as the methylxanthine of choice, accounting for >90% of methylxanthine use since 2007 and 96% of methylxanthine use in 2010 (**Figure 4**; available at www.jpeds.com). The use of multiple methylxanthines was common before 2001 and decreased substantially to <5% of all methylxanthine use after 2007. The percentage of VLBW infants exposed to caffeine therapy also increased over time, from 43% in 1999 to 73% in 2010 (**Figure 5**; available at www.jpeds.com). Similar trends were seen for extremely low birth weight (<1000 g) infants.

Discussion

In VLBW infants, early caffeine initiation was associated with reduced neonatal morbidity, including a decreased incidence of BPD and of PDA requiring treatment. In addition, the centers in this study have shifted toward earlier initiation of caffeine therapy over time, with a majority of VLBW infants receiving early caffeine therapy in 2010. Although the observational study design limits our ability to draw inferences regarding causality, the effect of early caffeine therapy on improving pulmonary outcomes in VLBW infants is biologically plausible. Caffeine rapidly improves several functions involved in effective respiration, including pulmonary compliance and airway resistance,[6,8] minute ventilation,[5] and respiratory muscle contractility.[7] Together, these benefits of caffeine therapy can facilitate earlier weaning from MV or increase the success of initial CPAP therapy and reduce ventilator-associated lung injury. This is particularly relevant in the early neonatal period, when the rate of failure of initial CPAP therapy is high and when apnea of prematurity–related symptoms may be prevalent.[20] The potential benefits of caffeine therapy in reducing ventilator-associated lung injury are supported by our finding of a 6-day reduction in the mean days on MV in the early caffeine group.

The association of caffeine therapy with a decreased incidence of PDA requiring treatment is also supported by a number of candidate biological mechanisms, including improvements in cardiac function,[21] altered fluid balance,[22] and effects on signaling pathways involved in ductal constriction.[23,24] Caffeine has been associated with increases in cardiac output and blood pressure in preterm infants[21] and adults.[25] In the present study, infants receiving early caffeine therapy received less pharmacologic treatment of hypotension. The decreased need for respiratory or cardiac support may reduce the likelihood of a clinician choosing to treat a PDA. In addition, excessive fluid intake in the first week of life is a risk factor for PDA,[26] and caffeine, through its diuretic properties,[22] may help optimize early fluid balance in VLBW infants. The increased weight loss observed in the first week of life in infants receiving early caffeine therapy may be a result of caffeine's diuretic effects or may be secondary to caffeine's effects on metabolic demands.[27] Regardless, the indications for treatment of PDA cannot be ascertained from this database and remain controversial in current neonatal practice.[28] Interestingly, infants in the early caffeine group had a lower incidence of PDA despite receiving less frequent treatment with prophylactic indomethacin, which is known to decrease the incidence of PDA.[29] This finding may suggest that centers (or clinicians) that used indomethacin prophylaxis were less likely to initiate early caffeine therapy.

Although not selected as prespecified outcome measures, decreased incidence of IVH and of ROP were seen in the early caffeine group. We speculate that the decreased incidence of ROP in the early caffeine group is a consequence of improved pulmonary morbidity and a decreased need for ventilation and exposure to supplemental oxygen. Severe ROP is also associated with intermittent hypoxia, which may be reduced by caffeine treatment.[30] In the CAP trial, infants allocated to receive caffeine had a lower incidence of severe ROP.

The association between early caffeine therapy and decreased IVH, including severe IVH, requires additional study. A potential mechanism behind this finding is caffeine's effect on decreasing cerebral blood flow,[31,32] which may better protect the germinal matrix from hemorrhage.

In our multicenter cohort, the indications for early caffeine therapy likely varied among the centers. Interestingly, although apnea symptoms are often reported and documented inconsistently, the incidence of early apnea was low in our cohort, implying that perhaps apnea was not a common indication for early initiation of caffeine treatment. In addition, more than 60% of infants in the early caffeine group received MV on DOL 1. Thus, we speculate that the infants receiving early caffeine therapy were treated prophylactically to prevent apnea or were treated to facilitate weaning from ventilation.

Although BPD prevention is not an accepted indication for caffeine use, we cannot exclude the possibility that some centers in this study might have used early caffeine therapy for this purpose.[33] We attempted to account for confounding variables related to the indication for early initiation of caffeine therapy by robustly controlling for factors that potentially could influence early therapy, including baseline and early respiratory support characteristics, through the use of PS matching. The association of early caffeine therapy and decreased BPD remained significant in PS-matched infants who had a similar GA, birth weight, sex, race, respiratory support, and maximal FiO_2 on DOL 1. Importantly,

these 6 variables are the primary predictors of the risk of BPD.[34] The similarity in each of these variables between the groups reassured us that PS-matched infants in the late caffeine group did not represent a population with a markedly increased or decreased baseline risk of BPD. In addition, several of these variables are primary determinants of neonatal mortality and long-term neurologic outcome.[35]

Infants receiving early caffeine, particularly those at <24 weeks GA, had a higher incidence of death. Although this finding is of potential concern, the lower mortality observed in the late caffeine group may be related to a survival bias. Mortality at this GA is high, and most deaths occur early after birth; for instance, an infant who received early caffeine (DOL 0-2) was at risk of dying on DOL 4. In contrast, an infant included in the late caffeine cohort who received caffeine on DOL 5 obviously could not have died on DOL 4. Further study is needed to confirm this finding in infants born at the earliest GAs.

This study has several limitations. Changes in clinical practice over the study period might have influenced the clinical outcomes. Recent data suggest a small decrease in the incidence of BPD over the last decade with no apparent decreases in mortality.[36,37] To account for these potential temporal changes in outcomes, we included birth year in our PS-matching model. Another limitation was our inability to use a physiological definition of BPD, which may be a more reliable measure of BPD in VLBW infants.[38] Owing to limitations in the data available to us, we were unable to capture all variables that might have influenced the indication for caffeine initiation or clinical outcomes. These include maternal variables, such as chorioamnionitis, and therapies, such as postnatal steroid use for the treatment of severe lung disease. In addition, the differences in hypotension requiring treatment, while possibly influenced by caffeine's effects on cardiac function,[21] might have been equally reflective of an increased severity of illness in infants receiving late caffeine therapy. The association between early caffeine initiation and reductions in various neonatal morbidities may have been affected by treatment and selection bias. Despite our attempts to address confounding factors, we were unable to account for all factors that might have influenced early caffeine therapy or were reflective of early severity of illness. In addition, it is important to note that the small sample sizes in the subgroup analyses might have limited our ability to detect clinically significant differences.

Our findings have important clinical and research implications for VLBW infants. This study demonstrates that caffeine is now widely used in preterm infants, with approximately 70% of all VLBW infants receiving therapy in 2008-2010. In addition, currently available therapies to decrease the burden of BPD and PDA are limited. Our findings are in line with observations from our previous single-center, retrospective study in which early caffeine therapy was also associated with a decreased incidence of BPD or death.[13] To our knowledge, these are the only studies to date to report an association between early caffeine therapy and reductions in BPD and in PDA requiring treatment.

Caffeine is already a widely used medication in VLBW infants, but optimizing caffeine therapy to maximize treatment effects may yield substantial benefits for VLBW infants at risk for BPD and PDA. Other potential benefits of early caffeine prophylaxis may include reduced risks of ROP and IVH. A change in practice toward earlier initiation of caffeine therapy is already occurring, but randomized controlled trials are needed to investigate the benefits and safety of early caffeine prophylaxis and its effect on short- and long-term outcomes. ■

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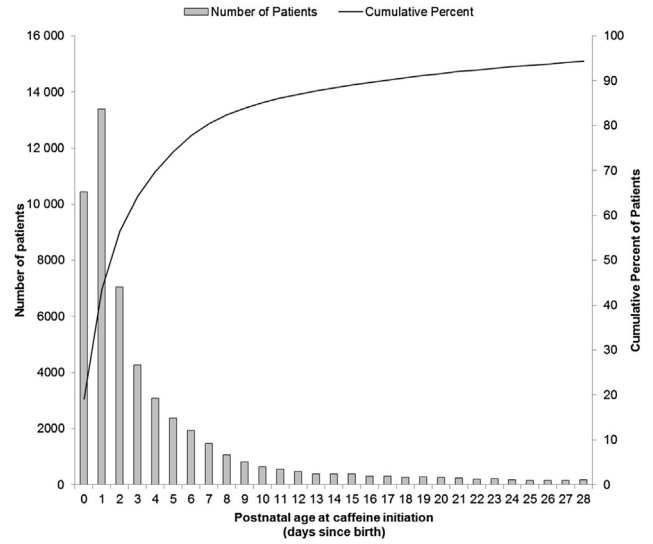

Figure 2. Distribution of infants receiving caffeine therapy by postnatal age at initiation. Data are presented for a total of 51 623 unmatched infants with birth weight <1500 g who received caffeine therapy. Infants with caffeine initiation beyond 28 DOL, representing 5.6% of all patients (n = 3084), are not depicted.

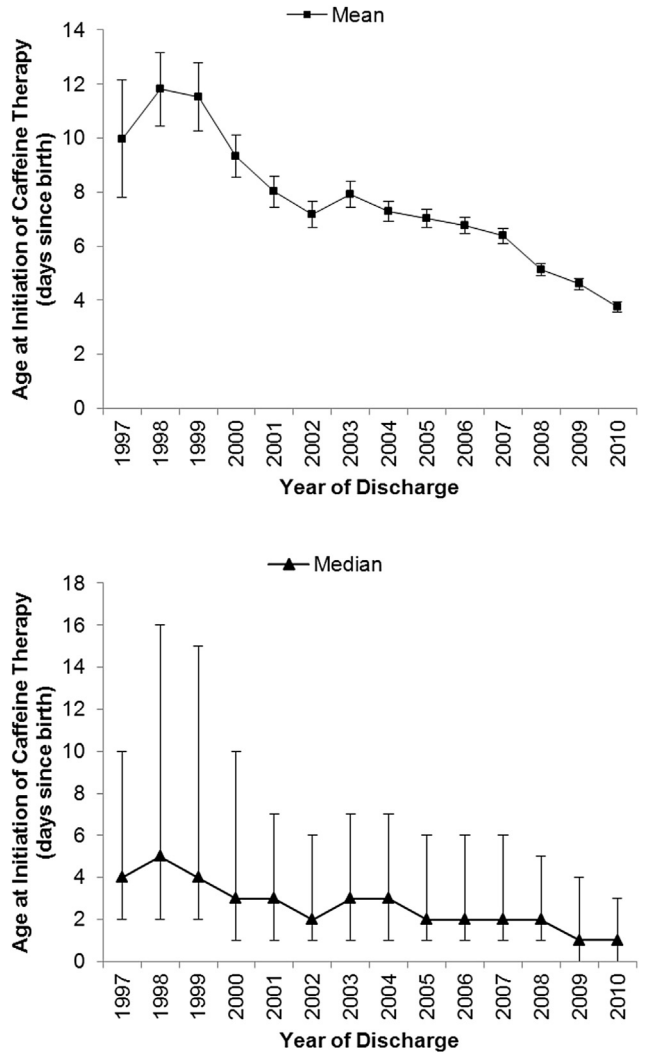

Figure 3. Mean and median postnatal age at caffeine initiation in VLBW infants, demonstrating a trend toward early initiation of caffeine therapy over time. R^2 = 0.89 for negative correlation between birth year and mean age at caffeine initiation. *Whisker bars* indicate 95% CI for mean values and IQR for median values.

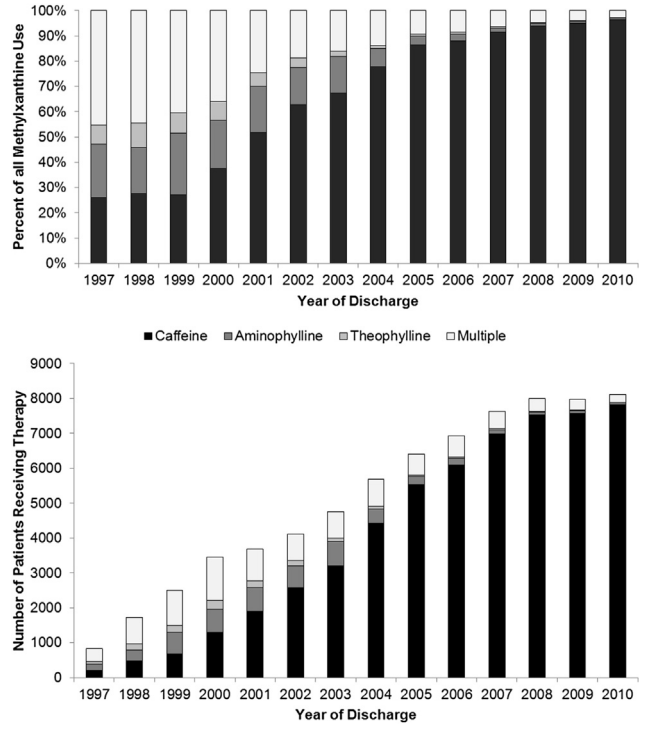

Figure 4. Percentage of VLBW infants receiving methylxanthine therapy as a fraction of overall methylxanthine use (*top*) and number of VLBW infants receiving methylxanthines (*bottom*). Exclusive use of caffeine increased from 26% in 1997 to 96% in 2010. Treatment with methylxanthines other than caffeine, including multiple methylxanthines, predominated before 2001 and was infrequent after 2007 (<5%).

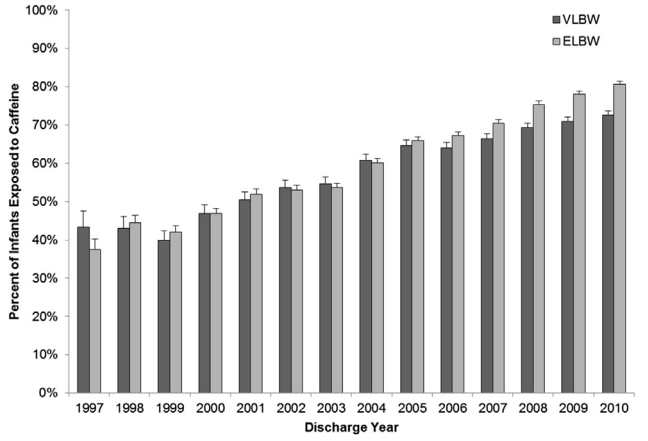

Figure 5. Percentages of VLBW and extremely low birth weight infants exposed to caffeine during hospitalization. *Whisker bars* indicate 95% CIs. *ELBW*, extremely low birth weight.

Table II. Respiratory support characteristics

Respiratory characteristics	PS-matched patients		
	Early caffeine (n = 14 523)	Late caffeine(n = 14 498)	*P* value
Characteristics at caffeine initiation			
Respiratory support at caffeine initiation, n (%)*			
Room air	1116 (7.7)	2624 (18.1)	<.0001
Hood oxygen	86 (0.6)	51 (0.4)	
Nasal cannula	509 (3.5)	1635 (11.3)	
High-frequency nasal cannula	609 (4.2)	1118 (7.7)	
CPAP	3131 (21.6)	2545 (17.6)	
MV	7562 (52.1)	5678 (39.2)	
HFOV	1510 (10.4)	847 (5.8)	
Maximal FiO_2 at caffeine initiation			
Mean (5th-95th percentile)	0.28 (0.21-0.50)	0.28 (0.21-0.50)	.97
Median (IQR)	0.21 (0.21-0.30)	0.22 (0.21-0.30)	
Characteristics at 36 0/7 weeks PMA†			
Infants evaluated at 36 0/7 weeks PMA, n	8879	9813	
Respiratory support at 36 0/7 weeks PMA, n (%)			
Room air	4949 (55.7)	4713 (48.0)	<.0001
Hood oxygen	68 (0.8)	163 (1.0)	
Nasal cannula	2439 (27.5)	3081 (31.4)	
High-frequency nasal cannula	482 (5.4)	656 (6.7)	
CPAP	522 (5.9)	639 (6.5)	
MV	375 (4.2)	565 (5.8)	
HFOV	44 (0.5)	64 (0.7)	
Receipt of FiO_2 >0.21, n (%)	3064 (34.8)	4150 (42.7)	<.0001
Receipt of FiO_2 >0.30, n (%)	1972 (22.4)	2653 (27.3)	<.0001

PMA, postmenstrual age.
*A total of 49 (0.2%) PS-matched patients with missing data.
†For the early caffeine group, 659 (4.5%) infants died before discharge, 4439 (30.5%) were evaluated before 36 weeks PMA, and 558 (3.8%) had missing data. For the late caffeine group, 542 (3.7%) infants died before discharge, 3707 (25.5%) were evaluated before 36 weeks PMA, and 473 (3.3%) had missing data.

Table V. Primary outcome by GA subgroup

GA	BPD in survivors			Death			BPD or death		
	Early caffeine, n (%)	Late caffeine, n (%)	OR (99% CI)	Early caffiene, n (%)	Late caffiene, n (%)	OR (99% CI)	Early caffiene, n (%)	Late caffiene, n (%)	OR (99% CI)
<24 wk	86 (43.7)	538 (67.1)	0.38 (0.25-0.58)	80 (33.2)	132 (15.3)	2.76 (1.77-4.28)	163 (82.7)	645 (80.4)	1.17 (0.68-2.08)
24-28 wk	4346 (29.0)	5996 (49.7)	0.41 (0.39-0.44)	927 (5.5)	745 (5.6)	0.99 (0.87-1.13)	5205 (34.8)	6592 (54.7)	0.44 (0.41-0.47)
29-32 wk	1274 (10.9)	1340 (17.2)	0.59 (0.53-0.66)	140 (1.1)	97 (1.2)	0.97 (0.69-1.36)	1395 (12)	1412 (18.1)	0.62 (0.55-0.68)
>32 wk	109 (7.3)	177 (13.4)	0.51 (0.36-0.71)	21 (1.4)	22 (1.6)	0.83 (0.38-1.84)	123 (8.2)	188 (14.2)	0.54 (0.39-0.74)

Data are from all patients (matched and unmatched).