JPPT | Clinical Investigation

Evaluation of Timing and Dosing of Caffeine Citrate in Preterm Neonates for the Prevention of Bronchopulmonary Dysplasia

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OBJECTIVE The aim of this study was to evaluate the timing and dosing of caffeine therapy in relation to the development of bronchopulmonary dysplasia (BPD).

METHODS This was a single-center, retrospective cohort study comparing early (days of life 0–2) to late (day of life 3 or greater) caffeine initiation in extremely low birth weight neonates, with a secondary analysis of large (10 mg/kg/day) to small dose (5 mg/kg/day) caffeine.

RESULTS There were 138 patients in the primary timing analysis. The early caffeine group had a lower incidence and reduced odds of the composite outcome of BPD or all-cause mortality, compared with the late caffeine group (64% vs. 88%, respectively; adjusted $p < 0.05$; adjusted OR 0.36 [95% CI 0.13–0.98]). No statistically significant difference was found between dosing groups ($p = 0.29$) in the primary outcome; however, there was a lower rate of patent ductus arteriosus requiring treatment ($p = 0.05$) and decreased likelihood of discharging home on oxygen ($p = 0.02$) in the large-dose group compared with the small-dose group.

CONCLUSIONS Early caffeine initiation significantly decreased the incidence of BPD or all-cause mortality in extremely low birth weight neonates. Patients receiving large-dose caffeine had improved secondary outcomes, although no difference in BPD was noted. Further studies are needed to determine the optimal dosing of caffeine.

ABBREVIATIONS BPD, bronchopulmonary dysplasia; DOL, day of life; ELBW, extremely low birthweight; NICU, Neonatal Intensive Care Unit; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; VLBW, very low birth weight

KEYWORDS bronchopulmonary dysplasia; caffeine citrate; neonatal outcomes; preterm neonates

J Pediatr Pharmacol Ther 2018;23(2):139–145

DOI: 10.5863/1551-6776-23.2.139

Introduction

Extremely low birth weight (ELBW) neonates, defined as infants weighing less than 1000 g at birth, carry the highest risk for experiencing apneic episodes during the neonatal period and for developing bronchopulmonary dysplasia (BPD). Poor outcomes have been associated with BPD, such as increased rates of hospitalization within the first year of life; chronic lung disease; poor growth and nutritional status; increased risk of cardiovascular sequelae, such as pulmonary arterial hypertension and systemic hypertension; and poor neurodevelopmental outcomes, including language delay and fine and gross motor impairment.[1]

Methylxanthine therapy has been the standard of care for the treatment and prevention of apnea of prematurity, with caffeine now being the most commonly used agent in this class.[2–5] Several mechanisms of action are described for methylxanthine prevention and treatment of apnea, including increased sensitivity to carbon dioxide, decreased muscle fatigability, elevated metabolic rate, enhanced catecholamine activity, increased diaphragmatic contractility, and increased diuresis via tubular adenosine A1 receptors.[5] Several studies have shown that caffeine therapy initiated during the first several days after birth in very low birth weight (VLBW) neonates reduces the risk of developing BPD, reduces time on mechanical ventilation, and overall improves neonatal outcomes.[2,3] Schmidt et al[4] also showed that caffeine improves long-term survival without neurodevelopmental disability in the VLBW population. Several studies have evaluated the early initiation of caffeine on neonatal outcomes, including BPD and all-cause mortality, and have shown that the initiation of caffeine within the first 2 days of life (DOLs) is associated with reduced incidence of the combined outcome of BPD and mortality compared with initiation at greater than DOL 2.[5–8] Other significant secondary findings from individual studies include decreased time on mechanical ventilation, decreased need for treatment of the patent ductus arteriosus (PDA), and

decreased incidence of retinopathy of prematurity (ROP).[5–8] Despite this evidence, many institutions have not yet adopted early caffeine as standard therapy.[7]

Additionally, some studies have tried to evaluate caffeine dosages and levels with regard to prevention of BPD, apnea of prematurity, and extubation[9,10]; however, the regimens used were different than the standard US dosing regimens. The typical dosing used at our institution is a loading dose of caffeine citrate 20 mg/kg followed by a maintenance dose range of 5 to 10 mg/kg/day. Although current evidence suggests that earlier and larger dosing of caffeine may be beneficial, no clear guideline exists for the exact timing and regimen to optimize the prevention of BPD. The primary purpose of this study was to determine whether initiation of early caffeine therapy (DOLs 0–2) in preterm neonates is associated with improved neonatal outcomes, specifically a combined outcome of BPD and all-cause mortality, compared with late caffeine therapy (DOL 3 or greater). The secondary purpose was to determine the relationship between caffeine dose and neonatal outcomes.

Materials and Methods

This study was a single-center, retrospective cohort study of ELBW neonates who were admitted to the University of Chicago Medicine Comer Children's Hospital Neonatal Intensive Care Unit (NICU) within 24 hours of birth between May 1, 2008, and April 15, 2014, received caffeine citrate, and had data from a previously conducted randomized controlled trial in our NICU (National Institutes of Health grant: NIH CTSA UL1 TR000430). Neonates who died within the first 24 hours after birth or had major congenital anomalies were excluded. This study was approved by the Institutional Review Board.

The primary objective compared initiation of early caffeine therapy (DOLs 0–2) to late caffeine therapy (DOL 3 or greater). The secondary objective compared a larger initial caffeine maintenance dose (10 mg/kg/day) to a smaller maintenance dose (5 mg/kg/day). All patients received a caffeine loading dose of 20 mg/kg. Patients were excluded from the dosing analysis if the same maintenance dose was not received during the first 7 days of treatment or if the dose varied from the predefined groups by greater than 1 mg/kg. Eligible patients were identified in the REDCap database from a previously randomized control trial (National Institutes of Health grant: NIH CTSA UL1 TR000430) and from an electronic report from the institutional electronic health record of caffeine use during the study period.

The primary outcome for both the primary and secondary objectives was the composite outcome of BPD or all-cause mortality. BPD was defined as an oxygen requirement at 36 weeks postmenstrual age (PMA). Secondary outcomes included all-cause mortality, hospital length of stay, PDA requiring treatment, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, ROP, days on mechanical ventilation, PMA of first successful extubation, duration of non-invasive respiratory support, duration of oxygen requirement, discharge home on oxygen, postnatal steroid use, culture-proven sepsis, weight gain, and postnatal age of reaching full feeds.

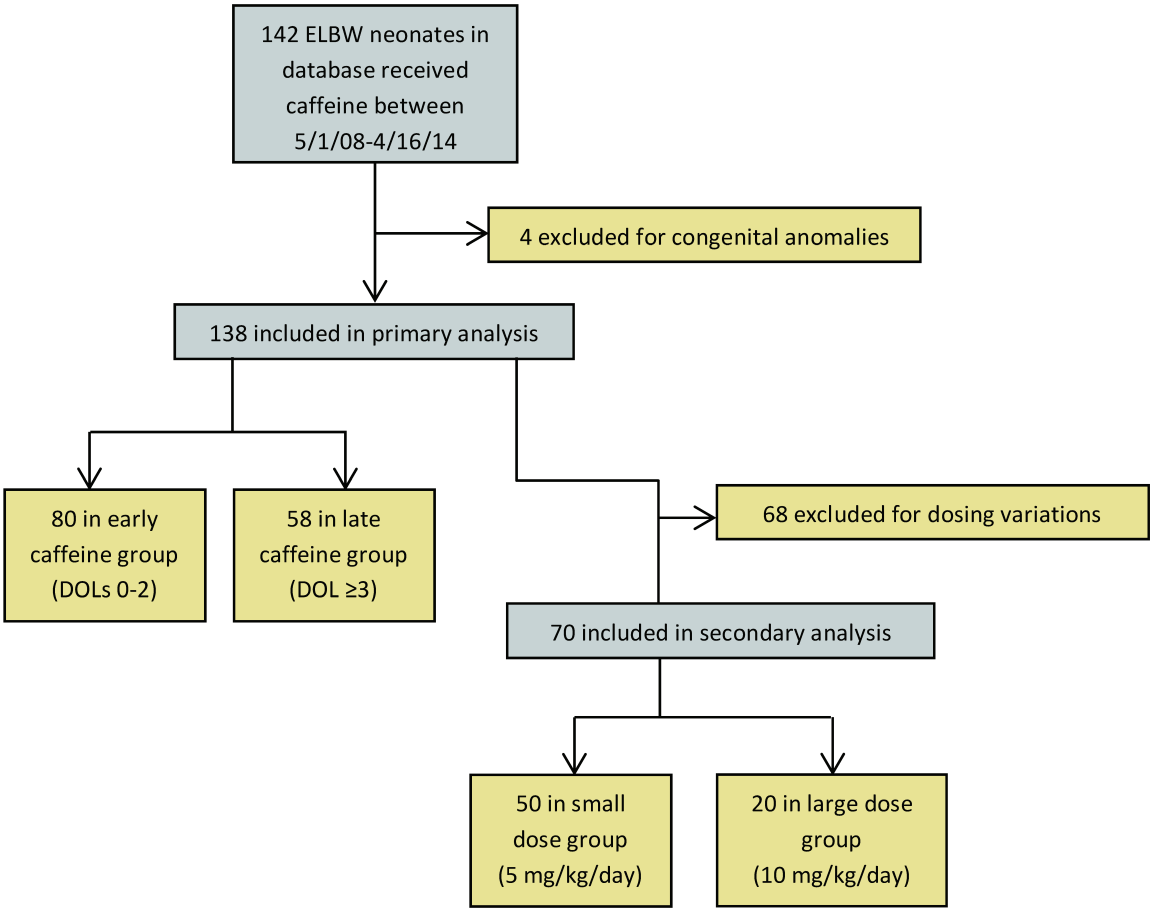
Statistical analyses were performed with STATA software Version 14 (STATA Corp, College Station, TX). Both groups in the primary and secondary analyses were compared using Pearson χ^2 test or Fisher exact test for categoric variables and the Wilcoxon rank sum test for continuous variables, because data were not normally distributed. Data were expressed in medians, IQRs, and proportions. Multivariate logistic regression analysis was performed to evaluate the effect of significant outcomes found in the univariate analysis of the early versus late caffeine groups, and the large dose versus small dose caffeine groups. Adjustments were made for clinically significant factors that might affect the development of BPD, including gestational age (GA), PDA requiring surgery or treatment, early-onset sepsis, and late-onset sepsis. All statistical analyses assumed a significance level of 0.05.

Results

There were 142 ELBW neonates in the REDCap database who received caffeine between May 1, 2008, and April 15, 2014. Four patients were excluded for congenital anomalies. A total of 138 patients were included in the primary analysis, with 80 in the early caffeine group and 58 in the late caffeine group. Of the 138 patients in the primary analysis, 68 were excluded from the secondary analysis because of dosing variations. The remaining 70 patients were included in the secondary analysis, with 20 in the large-dose group and 50 in the small-dose group (Figure).

Baseline demographics of the included patients in the primary and secondary analyses are listed in Table 1. Significant differences between groups in the primary analysis included a lower GA, lower birth weight, and higher incidence of mechanical ventilation on DOL 1 in the late caffeine group compared with the early caffeine group. In the secondary analysis, the large-dose group was more likely to have early-onset sepsis compared with the small-dose group. All other variables were similar between groups. With regard to caffeine therapy, the median DOL of caffeine initiation was 1 day (IQR, 1–1 days) versus 9.5 days (IQR, 5–43 days); the median initial maintenance dose was 5 mg/kg/day (IQR, 5–8 mg/kg/day) versus 5.1 mg/kg/day (IQR, 5–7.4 mg/kg/day); and the median PMA of caffeine discontinuation was 30.5 weeks (IQR, 28.7–31.7 weeks) versus 31.7 weeks (IQR, 30–33.5 weeks) in the early versus late caffeine groups, respectively. Similarly, the median DOL of caffeine initiation was 2 days (IQR, 1–6 days) versus 1.5 days (IQR, 1–7 days); the median initial caffeine maintenance dose was 5 mg/kg/day (IQR, 5–5 mg/kg/day) versus 10 mg/kg/day (IQR, 10–10 mg/kg/day); and

Figure. Diagram of cohort.



DOL, day of life; ELBW, extremely low birthweight

the median PMA of caffeine discontinuation was 30.5 weeks (IQR, 29–32.1 weeks) versus 31.3 weeks (IQR, 29.9–33.4 weeks) in the small-dose versus large-dose groups, respectively.

The composite outcome of BPD or all-cause mortality occurred in 51 of 80 patients (64%) in the early caffeine group compared with 51 of 58 patients (88%) in the late caffeine group (adjusted $p < 0.05$; adjusted OR 0.36 [95% CI, 0.13–0.98]; Table 2). This significant difference was also noted when evaluating the development of BPD alone, which occurred in 44 of 80 patients (55%) versus 48 of 58 patients (83%) in the early versus late initiation groups, respectively ($p = 0.001$). A total of 12 of 20 patients (60%) in the large-dose group experienced the composite outcome of BPD or all-cause mortality compared with 40 of 50 patients (80%) in the small-dose group (Table 3). This was not statistically significant, however, even after adjusting for confounders ($p = 0.29$). When evaluating the outcome of BPD alone, there was a significant difference in the univariate analysis, with an incidence of 10 of 20 (50%) versus 38 of 50 (76%) in the large-dose versus small-dose groups, respectively ($p = 0.03$), but this difference disappeared when potential confounding variables, such as GA, PDA requiring treatment after DOL 3, and early-onset sepsis were included in the model (adjusted OR 0.43 [95% CI, 0.12–1.47]).

In the primary analysis, the late caffeine group was more likely to have a longer length of stay, PDA requiring medical treatment or surgery, longer duration of mechanical ventilation and oxygen use, late-onset sepsis, higher postnatal steroid use, later PMA of first successful extubation, higher incidence of discharge home on oxygen, and later postnatal age of reaching full feeds ($p < 0.05$ for all variables; Table 4). The late caffeine group had a significantly higher rate of ROP, but this was no longer significant when adjusting for the significantly longer duration of oxygen requirement (unadjusted $p = 0.04$, adjusted $p = 0.98$). The secondary analysis had some differences in neonatal outcomes,

Table 1. Baseline Demographics

Characteristic	Caffeine Administration			Dose Caffeine		
	Early (n = 80)	Late (n = 58)	p value	Large Dose (n = 20)	Small Dose (n = 50)	p value
Gestational age, wk*	26.4 (25.3–27.4)	24.9 (24.1–26)	<0.001	26.1 (25.1–27)	25.6 (24.4–26.9)	0.39
Birth weight, g*	820 (755–910)	665 (575–790)	<0.001	768 (635–850)	788 (630–870)	0.76
Male, n (%)	43 (53.8)	25 (43.1)	0.22	9 (45)	26 (52)	0.6
African American, n (%)	53 (66.3)	42 (72.4)	0.52	13 (65)	28 (56)	0.58
Antenatal steroids, n (%)	63 (78.8)	52 (89.7)	0.09	16 (80)	43 (86)	0.72
Cesarean delivery, n (%)	53 (66.3)	42 (72.4)	0.44	11 (55)	37 (74)	0.12
Chorioamnionitis, n (%)	10 (12.5)	4 (6.9)	0.28	5 (25)	5 (10)	0.14
SGA, n (%)	19 (23.8)	20 (34.5)	0.17	9 (45)	14 (28)	0.17
Agpar score at 5 min*	7 (6–8)	7 (6–8)	0.44	7 (5.5–8)	7 (6–8)	0.74
Prophylactic indomethacin, n (%)	73 (91.3)	51 (87.9)	0.52	18 (90)	44 (88)	1.00
Mechanically ventilated on DOL 1, n (%)	53 (66)	56 (97)	0.001	13 (65)	40 (80)	0.3
Early-onset sepsis, n (%)	2 (2.5)	3 (5.2)	0.41	3 (15)	0 (0)	0.02

DOL, day of life; SGA, small for gestational age
* Median and IQR.

including a lower incidence of PDA requiring treatment (p = 0.05) and decreased likelihood of discharging home on oxygen (p = 0.02) in the large-dose group compared with the small-dose group (Table 4).

Discussion

Although previous studies support the early initiation of caffeine in preterm neonates for BPD prevention, no consensus has been made on the most appropriate regimen. These published studies that have focused on the timing of caffeine initiation have not addressed the dosing of the caffeine. Other studies have attempted to evaluate the relationship between caffeine dose and BPD prevention. This includes a study by Alur et al[9] that evaluated serum caffeine concentrations and found that higher concentrations were associated with a reduced incidence of chronic lung disease, which included BPD,[9] and a study by Mohammed et al[10] that found a reduced incidence of apnea of prematurity and reduced incidence of extubation failure with larger doses. The aim of this study was to add to the existing literature by evaluating both the timing and dosing of caffeine for BPD prevention, specifically in the ELBW population. We found that early initiation of caffeine within DOLs 0 to 2 led to a significant decrease in the composite outcome of BPD or all-cause mortality and BPD alone. Early caffeine initiation was also associated with decreases in the incidence of PDA requiring medical treatment or surgery, requirement for postnatal steroid use, length of stay, late-onset sepsis, duration of mechanical ventilation and oxygen requirement, and discharge home on oxygen, and it was associated with successfully extubating and reaching full feeds earlier. These secondary outcomes are likely influenced, however, by the differences between groups regarding GA and birth weight.

Since the study by Schmidt et al[3] was published in 2006, it appears that more NICUs have been administering early caffeine for very preterm neonates to prevent apnea of prematurity.[5] More hospitals also have been attempting to extubate patients earlier with concomitant use of caffeine, with some evidence showing decreased rates of re-intubation.[11] These practices may additionally lead to a decrease in duration of me-

Table 2. Primary Outcome for Primary Analysis

Outcomes	Early Group, n (%); n = 80	Late Group, n (%); n = 58	p value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Composite of BPD or all-cause mortality	51 (64)	51 (88)	0.001 (unadjusted) <0.05 (adjusted)	0.24 (0.1–0.6)	0.36 (0.13–0.98)
BPD	44 (55)	48 (83)	0.001	0.25 (0.11–0.57)	0.36 (0.15–0.87)
All-cause mortality	8 (10)	5 (9)	1	—	—

BPD, bronchopulmonary dysplasia; —, not done

Table 3. Primary Outcome for Secondary Analysis

Outcomes	Large Dose, n (%); n = 20	Small Dose, n (%); n = 50	p value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Composite of BPD or all-cause mortality	12 (60)	40 (80)	0.29	0.38 (0.12–1.16)	0.49 (0.13–1.82)
BPD	10 (50)	38 (76)	0.03	0.31 (0.10–0.93)	0.43 (0.12–1.47)
All-cause mortality	3 (15)	3 (6)	0.34	—	—

BPD, bronchopulmonary dysplasia; —, not done

chanical ventilation, which may explain the findings in our study of decreased incidence of BPD or all-cause mortality and of BPD alone in the early caffeine group (64% vs. 88%, adjusted $p < 0.05$). Similar results were reported by Lodha et al,[5] which was a large retrospective database study that showed a decreased incidence of BPD or all-cause mortality with early caffeine versus late caffeine in neonates born 31 weeks GA or less (adjusted OR 0.81 [95% CI 0.67–0.98]). Similar to our study, they also found that the late caffeine group required a longer duration of both mechanical ventilation ($p < 0.01$) and non-invasive respiratory support ($p < 0.02$).[5] Dobson et al[7] found a decreased incidence of BPD or all-cause mortality (27.6% vs. 34%, $p < 0.001$) with early caffeine versus late caffeine, respectively, in a large retrospective database study of VLBW neonates. Other significant findings included a decreased incidence of PDA treatment (12.3% vs. 19%, $p < 0.001$) and duration of mechanical ventilation ($p < 0.001$). Patel et al[6] also found a reduction in BPD or all-cause mortality with early caffeine (25%) versus late caffeine (53%, $p < 0.01$) in a retrospective cohort study of 140 VLBW neonates. It was also noted that the early caffeine group had a lower incidence of PDA requiring treatment compared with the late group (10% vs. 36%, $p = 0.01$). This finding was consistent with our results for PDA requiring medical treatment (26.3% vs. 58.6%, $p = 0.001$) or surgery (5% vs. 25.9%, $p = 0.001$) in the early versus late caffeine groups, respectively. The mechanism of this effect is not completely understood but may be related to increased cardiac output and blood pressure, improved pulmonary mechanics, and diuresis.[6,12,13]

To the best of our knowledge, this is the first US study that has compared large-dose versus small-dose caffeine in ELBW neonates with regard to the composite outcome of BPD or all-cause mortality. In Egypt, Mohammed et al[10] compared large dose (40 mg/kg loading dose with 20 mg/kg/day maintenance) and small dose (20 mg/kg loading dose with 10 mg/kg/day maintenance) in a prospective trial of 120 preterm neonates born less than 32 weeks GA who had experienced apnea by DOL 10. The authors found that the large-dose group had a significant decrease in extubation failure compared with the small-dose group (22% vs. 47%, respectively; $p = 0.02$), as well as a reduction in duration of oxygen therapy ($p = 0.04$).[10] In our study, we did not find a statistically significant difference in the incidence of the combined outcome of BPD or all-cause mortality between the small-dose versus large-dose groups (80% vs. 60%; $p = 0.29$). However, the sample size of the caffeine dosing groups was small and could have limited the ability to detect a statistically significant difference. We did find that there was a significantly lower incidence of BPD alone with the large-dose group; however, this no longer remained significant after adjusting for confounders. Another notable respiratory finding was that patients in the large-dose group were less likely to be discharged home on oxygen. Unfortunately, because a large portion of the patients were excluded from the secondary analysis for dosing variations, results are limited at this time. Further studies, including large randomized controlled trials, would be needed to fully evaluate the outcome of BPD or all-cause mortality for variations in dosing regimens.

There are several limitations to this study. Because of the retrospective nature of the study, there may be prescribing bias from the various NICU providers for which we could not completely account. Because of large variations in dosing, a significant number of patients were excluded from the secondary analysis, which may have increased the risk of a type II error. This was a single-center study, which may limit the external validity, with the exception of other NICUs with a similar population. Additionally, the vast majority of the included patients were born earlier in the study period between 2008 and 2012, thus limiting the results because it is difficult to know whether there have been any changes in BPD management since this time frame that may have affected the results of this study. Lastly, the 2 groups in the primary analysis were not matched in terms of GA, birth weight, or mechanical ventilation on DOL 1. Although the primary outcome of BPD or all-cause mortality was adjusted for significant variables, this variance limits the ability to fully assess differences in outcomes between groups.

This study adds to the existing literature that early initiation of caffeine within the first 2 days after birth is associated with a significant decrease in BPD or all-cause mortality, whereas the composite outcome of BPD or all-cause mortality did not differ between dosing groups. Despite this, further investigation into the use of larger-dose caffeine is warranted because of the already well-established safety profile of this larger

Table 4. Secondary Outcomes

Characteristic	Caffeine Administration			Large Versus Small Dose		
	Early (n = 80)	Late (n = 58)	p value	Large (n = 20)	Small (n = 50)	p value
Length of stay, days*	91 (68–118)	118 (94–154)	<0.001	110 (93–133)	108 (79–135)	0.7
Patent ductus arteriosus requiring treatment ≥DOL 3, n (%)	21 (26.3)	34 (58.6)	0.001	3 (15)	21 (42)	0.05
Patent ductus arteriosus requiring surgery, n (%)	4 (5)	15 (25.9)	0.001	1 (5)	6 (12)	0.67
Intraventricular hemorrhage, n (%)	17 (21.3)	18 (31)	0.19	4 (20)	15 (30)	0.55
Periventricular leukomalacia, n (%)	6 (7.5)	6 (10.3)	0.56	1 (5)	6 (12)	0.66
Necrotizing enterocolitis, n (%)	10 (12.5)	13 (22.4)	0.12	5 (25)	6 (12)	0.27
Retinopathy of prematurity, n (%)	39 (48.8)	40 (68.9)	0.04 (unadjusted) 0.98 (adjusted)	14 (70)	29 (58)	0.92
Mechanical ventilation, days*	35 (10–52)	63 (46–76)	<0.001	48 (39–70)	47 (23–71)	0.74
Duration of oxygen requirement*, days	73 (49–105)	111 (93–146)	<0.001	90 (61–117)	104 (68–128)	0.54
Late onset sepsis, n (%)	35 (43.8)	37 (74.1)	0.02	11 (55)	22 (44)	0.41
Postnatal steroid use, n (%)	27 (33.8)	43 (74.1)	0.001	11 (55)	25 (50)	0.79
PMA of first successful extubation, wk*	30.8 (28.5–33.1)	33.4 (31.4–36.2)	<0.001	33.2 (30.6–34.5)	32.4 (30–35.1)	0.63
Duration of non-invasive respiratory support, days*	46 (32–57)	49 (27–66)	0.45	44 (20-53)	51 (37–66)	0.07
Discharged home on oxygen, n (%)	22 (27.5)	34 (58.6)	<0.001	5 (25)	28 (56)	0.02
Weight gain between DOLs 0 and 6, g/kg/day*	1.3 (0–10.7)	2.5 (0–10.7)	0.87	1.8 (0–15.4)	0.35 (0–7.1)	0.55
Weight gain between DOLs 7 and 13, g/kg/day*	11.4 (7.1–17.1)	9.7 (0–16.4)	0.1	7.9 (1.5–18.8)	13.6 (7.1–18.6)	0.25
Weight gain between DOLs 14 and 20, g/kg/day*	10.7 (6.4–21.4)	12.9 (4.3–19)	0.72	8.3 (4.4–14.3)	13.9 (5–21.4)	0.16
Weight gain between DOLs 21 and 27, g/kg/day*	15.7 (6.4–21.4)	15.7 (6.4–24.3)	0.88	14.3 (6.1–20)	15.7 (4.3–22.9)	0.71
Postnatal age of reaching full feeds, days*	40 (27–59)	53 (34–73)	0.02	35 (22–47)	42 (28–61)	0.14

DOL, day of life; PMA, postmenstrual age

* Median and IQR.

dosage as well as data indicating potential benefit with larger doses. Large, randomized, multicenter controlled trials are needed to further evaluate the optimal caffeine timing and dosing for the prevention of BPD and all-cause mortality in this high-risk neonatal population.

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Disclosures The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Accepted October 13, 2017

REFERENCES

1. Kair LR, Leonard DT, Anderson JM. Bronchopulmonary dysplasia. *Pediatr Rev*. 2012;33(6):255–263.
2. Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev*. 2010;(1):CD000273.
3. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354(20):2112–2121.
4. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357(19):1893–1902.
5. Lodha A, Seshia M, Mcmillan DD, et al. Association of early caffeine administration and neonatal outcomes in very preterm neonates. *JAMA Pediatr*. 2015;169(1):33–38.
6. Patel RM, Leong T, Carlton DP, et al. Early caffeine therapy and clinical outcomes in extremely preterm infants. *J Perinatol*. 2013;33(2):134–140.
7. Dobson NR, Patel RM, Smith PB, et al. Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. *J Pediatr*. 2014;164(5):992e3–998e3.
8. Taha D, Kirkby S, Nawab U, et al. Early caffeine therapy for prevention of bronchopulmonary dysplasia in preterm infants. *J Matern Fetal Neonatal Med*. 2014;27(16):1698–1702.
9. Alur P, Bollampalli V, Bell T, et al. Serum caffeine concentrations and short-term outcomes in premature infants of ≤29 weeks of gestation. *J Perinatol*. 2015;35(6):434–438.
10. Mohammed S, Nour I, Shabaan AE, et al. High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial. *Eur J Pediatr*. 2015;174(7):949–956.
11. Steer PA, Flenady VJ, Shearman A, et al. Periextubation caffeine in preterm neonates: a randomized dose response trial. *J Paediatr Child Health*. 2003;39(7):511–515.
12. Gillot I, Gouyon JB, Guignard JP. Renal effects of caffeine in preterm infants. *Biol Neonate*. 1990; 58(3): 133–136.
13. Soloveychik V, Bin-Nun A, Ionchev A, et al. Acute hemodynamic effects of caffeine administration in premature infants. *J Perinatol*. 2009; 29(3): 205–208.