Original Investigation

Effects of Caffeine on Intermittent Hypoxia in Infants Born Prematurely
A Randomized Clinical Trial

Lawrence M. Rhein, MD; Nicole R. Dobson, MD; Robert A. Darnall, MD; Michael J. Corwin, MD; Tim C. Heeren, PhD; Christian F. Poets, MD; Betty L. McEntire, PhD; Carl E. Hunt, MD; and The Caffeine Pilot Study Group

IMPORTANCE Preterm infants have immature respiratory control and resulting intermittent hypoxia (IH). The extent of IH after stopping routine caffeine treatment and the potential for reducing IH with extended caffeine treatment are unknown.

OBJECTIVES To determine (1) the frequency of IH in premature infants after discontinuation of routine caffeine treatment and (2) whether extending caffeine treatment to 40 weeks' postmenstrual age (PMA) reduces IH.

DESIGN, SETTING, AND PARTICIPANTS A prospective randomized clinical study was conducted at 16 neonatal intensive care units in the United States, with an 18-month enrollment period. Preterm infants (<32 weeks' gestation) previously treated with caffeine were randomized to extended caffeine treatment or usual care (controls) at a PMA of at least 34 weeks but less than 37 weeks. Continuous pulse oximeter recordings were obtained through 40 weeks' PMA. Oximeter data were analyzed by persons masked to patient group.

INTERVENTION Continued treatment with caffeine.

MAIN OUTCOMES AND MEASURES Number of IH events and seconds with less than 90% hemoglobin oxygen saturation ($Sa0_2$) per hour of recording.

RESULTS Our analysis included 95 preterm infants. In control infants, the mean (SD) time at less than 90% $Sa0_2$ at 35 and 36 weeks' PMA was 106.3 (89.0) and 100.1 (114.6) s/h, respectively. The number of IH events decreased significantly from 35 to 39 weeks' PMA ($P = .01$). Extended caffeine treatment reduced the mean time at less than 90% $Sa0_2$ by 47% (95% CI, −65% to −20%) to 50.9 (48.1) s/h at 35 weeks and by 45% (95% CI, −74% to −17%) to 49.5 (52.1) s/h at 36 weeks.

CONCLUSIONS AND RELEVANCE Substantial IH persists after discontinuation of routine caffeine treatment and progressively decreases with increasing PMA. Extended caffeine treatment decreases IH in premature infants.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01875159

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Caffeine Pilot Study Group members are listed at the end of this article.

Corresponding Author: Carl E. Hunt, MD, Department of Pediatrics, Uniformed Services University of Health Sciences, 4301 Jones Bridge Rd, Bldg C-1069, Bethesda, MD 20814-4799 (carl.hunt@usuhs.edu).

JAMA Pediatr. 2014;168(3):250-257. doi:10.1001/jamapediatrics.2013.4371
Published online January 20, 2014.

Intermittent hypoxia (IH) is defined as brief, repetitive cycles of decreases in hemoglobin oxygen saturation (Sa) from a normoxic baseline, followed by reoxygenation and return to normoxia.[1] Many animal and human studies have established that IH, compared with chronic sustained hypoxia, is proinflammatory. Exposure to IH results in multiple impairments in many physiologic systems, including cardiorespiratory control,[2-4] sleep fragmentation, neuropathologic and neurocognitive deficits,[1,5-7] decreased neuronal integrity,[8] and apoptosis.[9-11]

Intermittent hypoxia is typically not apparent clinically and hence requires continuous physiologic recording for detection.[12] Immature respiratory patterns and resulting IH can continue until term-equivalent age and beyond for premature infants, even after resolution of clinical symptoms and discharge to home.[13-16]

Data confirming the short-term clinical significance of episodes of IH in preterm infants are limited. Recent studies, however, have noted an association between IH and severity of retinopathy of prematurity.[12] Later assessments of neurodevelopmental impairment in premature infants have shown impairments associated with frequent recurrent decreases in Sa_{O_2} at term-equivalent age and in early infancy.[17,18]

Caffeine is a respiratory stimulant that reduces the incidence of apnea and ameliorates or eliminates the clinical symptoms associated with apnea of prematurity.[19-22] However, we are unaware of any data based on continuous recordings of Sa_{O_2} and heart rate to document the extent of IH in preterm infants after routine clinical treatment with caffeine is discontinued, and there are no data indicating to what extent caffeine treatment may reduce the frequency and severity of IH as infants approach term-equivalent age.

We hypothesized that (1) IH is frequent in infants born prematurely after routine clinical caffeine treatment is discontinued and (2) extending caffeine treatment significantly reduces the frequency and severity of IH.

Methods

This multicenter prospective, randomized trial included 16 sites, with infants enrolled from July 2010 through December 2011.

Patients

Eligibility criteria for enrollment included (1) preterm birth at 25 weeks' plus 0 days ($25^{0/7}$) to $32^{0/7}$ weeks' gestational age (GA); (2) history of treatment with caffeine; (3) current postmenstrual age (PMA) of at least 33 weeks; (4) no current intubation, supplemental oxygen, or nasal airflow therapy; (5) no congenital or genetic disorder; and (6) no severe intraventricular hemorrhage (grade 3 or 4) or confirmed central nervous system infection. Institutional review board approval was obtained at each participating site. Written informed parental consent was obtained for each infant enrolled.

Study Protocol

Eligible infants were enrolled once they were breathing room air and the clinical team caring for the infant had discontinued caffeine treatment at least 1 day earlier. Once infants were enrolled, continuous physiologic recordings were initiated using a pulse oximeter with 2-second averaging for recording (Masimo Rad8). All oximeters were equipped with a serial data recorder (Acumen Instruments Corp) to allow continuous data storage on flash cards. Oximeters were set in the sleep mode, with no alarms for saturation or heart rate and no visual displays on the front panel. The only user alerts for the oximeters were for "probe off" and "low battery." Desaturation events with poor signal, identified by the data analysis software (ie, SIQ [signal indicator quality] ≤0.3), or a low-perfusion tag were considered artifact and excluded.[23]

As soon as clinical caffeine treatment had been discontinued for 5 days and their PMA was 34 to 37 weeks, infants were randomized either to receive the study caffeine protocol or to continue with usual care (controls). The decision to discontinue routine caffeine treatment and the exact timing of discontinuation was completely at the discretion of the clinical team and not dictated by the study protocol. The group randomized to receive the study caffeine protocol was given an oral loading dose of caffeine citrate (20 mg/kg) followed by an oral maintenance dosage of 6 mg/kg/d. No caffeine levels were obtained as part of this study. Because IH is not associated with clinical symptoms and hence not anticipated to affect clinical management differentially between the extended caffeine and usual-care (control) groups and because all analyses of outcome measures were to be performed by persons masked to treatment assignment, the control group did not receive a placebo.

For both treatment groups, we obtained continuous oximeter recordings until the infant was home for at least 1 week and had reached a PMA of at least 40 weeks. While infants were in the neonatal intensive care unit (NICU), health care providers were instructed to use the oximeter continuously whenever clinically feasible. At home, parents were instructed to use the oximeter during all sleep and quiet awake periods.

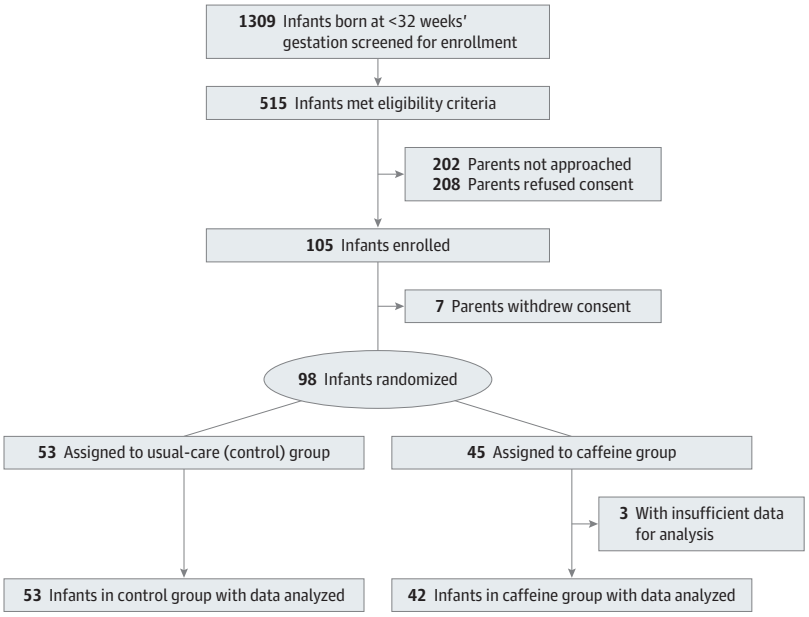
Outcome Measures

An *IH event* was defined as a decline in Sa_{O_2} by at least 5% from baseline to less than 90% that lasted at least 5 seconds. The primary outcome measures included (1) the number of IH events per hour of recording and (2) seconds with less than 90% Sa_{O_2} per hour of recording. Both outcomes were analyzed for each PMA week (ie, $36^{0/7}$-$36^{6/7}$, $37^{0/7}$-$37^{6/7}$, etc). We also measured the seconds with less than 85% or less than 80% Sa_{O_2} per hour of recording. Because the prevalence of most morbid conditions associated with prematurity is higher in extremely premature infants, we divided the 95 infants into 2 subgroups based on GA at birth for a post hoc secondary analysis. The median age at birth was 29.5 weeks, and the 2 subgroups were thus less than and more than 29.5 weeks' GA. We did not collect data on events related to apnea of prematurity recorded or observed by NICU staff before study enrollment.

Statistical Analysis

The final sample size of 100 infants was based on an interim analysis performed after the first 20 infants were enrolled. This sample size provided more than 80% probability of detecting at least a 36% reduction in IH events per hour of recording and

Figure 1. Flow Diagram of Study



Flow diagram from initial screening to enrollment, randomization, and completion of study.

in seconds with less than 90% Sao_2 per hour of recording. We used a block randomization design for each site to ensure balanced distribution of treatment groups. Twins and triplets were included, but all siblings were randomized to the same treatment regimen. For infants to be included in the final analysis for that PMA week, at least 10 hours of recorded data needed to be available.

Baseline characteristics and the extent and quality of pulse oximeter data in the caffeine and control groups were compared using the independent sample test for continuous measures and the χ^2 test for categorical measures. The number of IH events per hour of recording per week of PMA was compared using generalized estimating equation gamma regression models for longitudinal count data. Gamma regression models are appropriate for highly skewed measurement or count outcome data, and exponentiating the regression parameters from these models gives estimates of the percentage change in mean outcome corresponding to a change in the independent variable. Time (PMA in weeks) was represented in this model through a series of indicator variables, and we included interaction terms between study group and time in the model to account for a diminishing caffeine effect at later ages. Generalized estimating equation gamma regression models were also used to examine caffeine effects on time with Sao_2 below thresholds of 90%, 85%, and 80%.

We used generalized estimating equation gamma regression models to account for clustering due to longitudinal data (repeated observations from each infant over time). We also included sets of twins and triplets in our analyses, and sibships introduced a second source of clustering. The generalized estimating equation gamma regression procedure in SAS software (SAS Inc) accommodates clustering only on a single factor, so we explored the effect of including twin and triplet siblings in our findings by repeating the analyses including only the firstborn infant from each set of twins or triplets. Differences were considered statistically significant at $P < .05$.

Results

We enrolled 105 infants (**Figure 1**). No data were collected in 3 infants owing to early withdrawal of parental consent and in 4 other infants owing to withdrawal of consent before randomization, and data were insufficient for analysis in 3 other infants owing to equipment failure or user error. Our final study population for analysis thus included 95 infants from 80 families, including 2 sets of triplets, 11 sets of twins, and 56 singleton infants. There were 42 infants in the caffeine group and 53 in the control group, the difference being due in part to all twins or triplets from a family being enrolled in the same cohort. The maternal and infant demographic data and baseline variables are summarized in **Table 1** for the caffeine and usual-care groups. There were no statistically significant differences between the caffeine and usual-care groups in birth weight, GA at birth, PMA at the time of randomization or discharge, race, parity, or maternal education. However, the mean maternal age was lower in the extended caffeine treatment group ($P = .04$). We obtained 25 974 hours of analyzable oximeter data, representing 65% of the total hours of recording. The remaining data were excluded due to inadequate signal quality, as described in the Methods section. Because limited data were available before PMA week 35 and after PMA week 39, our analyses were restricted to PMA weeks 35, 36, 37, 38, and 39 (**Table 2**).

Occurrence of IH in Control Infants

Infants in the control group had a mean (SD) of 8.4 (8.4) episodes of IH per hour of recording at 35 weeks' PMA, which pro-

Table 1. Infant and Maternal Characteristics for the Total Sample

Characteristic	Caffeine (n = 42)	Usual Care (n = 53)
Gestational age, mean (SD), wk	28.6 (1.7)	29.1 (1.7)
Birth weight, mean (SD), g	1262.1 (265.6)	1274.5 (270.3)
Male infants, No. (%)	24 (57)	27 (51)
PMA at randomization, mean (SD), wk	35.6 (1.1)	35.4 (1.1)
PMA at discharge, mean (SD), wk	37 (1.6)	37.1 (1.8)
Maternal age, mean (SD)[a]	29.7 (6.5)	32.7 (6.9)
Maternal race, No. (%)		
White	27 (64)	42 (79)
Black or African American	11 (26)	9 (17)
Hawaiian or Pacific Islander	2 (5)	0
Other/refused	2 (5)	2 (4)
Hispanic		
Yes	2 (5)	8 (15)
No	38 (90)	45 (85)
Unknown	2 (5)	0
No. of births, mean (SD)	2.4 (1.1)	2.1 (1.0)
Singleton pregnancy, No. (%)	26 (62)	30 (57)
Marital status, No. (%)		
Never married	6 (14)	13 (25)
Married	30 (71)	33 (62)
Separated or divorced	2 (5)	2 (4)
Unknown	4 (10)	5 (9)
Educational level, No. (%)		
Less than high school	2 (5)	6 (11)
High school/GED	11 (26)	6 (11)
Some college	5 (12)	8 (15)
College graduate	11 (26)	15 (28)
Graduate school	8 (19)	11 (21)
Unknown	5 (12)	7 (13)

Abbreviations: GED, General Education Development; PMA, postmenstrual age.

[a] Data missing for 8 study infants.

Table 2. Analyzable Pulse Oximeter Recording by PMA

PMA, wk	Analyzable Recordings, h (% Total for Week)	
	Usual Care	Caffeine
34	603.0 (86.8)	429.7 (93.4)
35	2172.4 (82.4)	1730.2 (82.8)
36	3271.5 (75.8)	1816.9 (73.5)
37	3617.9 (68.6)	2754.6 (69.5)
38	2474.5 (63.9)	2340.9 (62.0)
39	1598.3 (53.2)	1790.5 (51.9)
40	398.3 (36.0)	435.0 (26.3)
41	272.4 (60.8)	184.0 (52.0)

Abbreviation: PMA, postmenstrual age.

gressively declined to 3.0 (3.3) episodes per hour by 39 weeks (P = .01) (**Table 3**). With a similar pattern, the time with less than 90%, less than 85%, or less than 80% Sao_2 (in seconds per hour of recording) also declined with increasing PMA. The post hoc analysis stratifying by the median GA at birth did not suggest major differences between the 2 subgroups (data not shown), but the study had limited power to assess differences between the 2 subgroups.

Effect of Extended Use of Caffeine on IH

Extended use of caffeine in the total sample had a beneficial effect on IH compared with usual care (Table 3). At 35 weeks' PMA, infants in the caffeine group had a 52% reduction in IH compared with the usual-care control group (95% CI, −70% to −22%). At 36 weeks, infants in the caffeine group had a 46% reduction (95% CI, −65% to −11%). Similarly, the time with less than 90% Sao_2 was 47% lower (95% CI, −65% to −20%) at 35 weeks for those receiving extended caffeine treatment and 45% lower (95% CI, −74% to −17%) at 36 weeks. There was no significant reduction in IH events per hour or in time with less than 90% Sao_2 at week 37, 38, or 39. The effect of extended caffeine treatment was consistent regardless of whether the Sao_2 threshold was set at 90%, 85%, or 80% (Table 3 and **Figure 2**). As in the control group total sample analysis, the post hoc analysis stratifying by the median GA at birth did not indicate major differences between the 2 subgroups (data not shown).

Repeating the analysis with only the firstborn infant from each twin or triplet set gave similar results. Extended caffeine treatment was associated with significant reductions in the number of IH events and seconds per hour with low Sao_2 at 35 and 36 weeks.

In 5 of the infants randomized to caffeine, caffeine treatment was discontinued because of tachycardia at the discretion of the clinical team. No other adverse events were related to caffeine use. There were no parental reports after discharge of any cyanotic or other events of concern related to the study protocol or oximeter recordings. After completion of the study protocol, 1 infant in the control group had an unrelated serious adverse event requiring rehospitalization for an apparent life-threatening event.

Discussion

The results of this study document several key findings regarding IH in infants born prematurely. Intermittent hypoxia occurs frequently in preterm infants after cessation of any clinically apparent apnea-associated symptoms and routine caffeine treatment and occurred in all enrolled infants. Our study also provides quantitative data to confirm that IH diminishes with increasing postnatal age. Regardless of the Sao_2 threshold used, the duration of IH (in seconds per hour) decreased by approximately 50% between 35 and 39 weeks' PMA.

The second primary finding from this study is that extended duration of treatment with caffeine beyond current routine clinical practice in the NICU decreases the frequency and severity of IH (Table 3). This decrease is qualitatively similar regardless of whether the threshold for IH is an Sao_2 of less than 90%, less than 85%, or less than 80% (Figure 2).

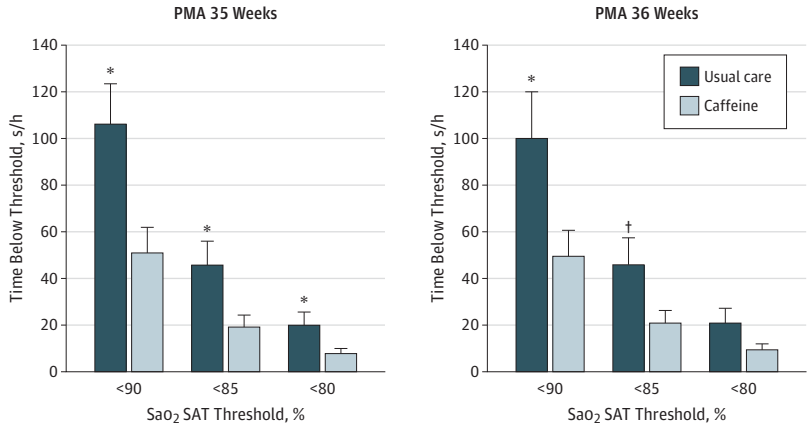
Table 3. Intermittent Hypoxia Measures and Percentage Change for Each Week of PMA for the Total Sample by Treatment Group[a]

	Week 35 PMA		Week 36 PMA		Week 37 PMA		Week 38 PMA		Week 39 PMA	
Measure	Caffeine	Usual Care	Caffeine	Usual Care	Caffeine	Usual Care	Caffeine	Usual Care	Caffeine	Usual Care
Events per hour of recording										
No., mean (SD)	3.6 (4.3)	8.4 (8.4)	3.8 (4.5)	8.2 (11.5)	4.3 (5.9)	5.2 (6.8)	4.2 (5.7)	4.7 (6.1)	2.2 (2.4)	3.0 (3.3)
Change (95% CI), %	−52 (−70 to −22)	...	−46 (−65 to −11)	...	−14 (−53 to 57)	...	−2 (−51 to 93)	...	−20 (−58 to 53)	...
<90% Sao_2 threshold										
Time, mean (SD), s/h	50.9 (48.1)	106.3 (89.0)	49.5 (52.1)	100.1 (114.6)	58.8 (74.1)	66.8 (75.2)	69.3 (108.8)	66.0 (74.8)	37.3 (40.4)	46.4 (47.0)
Change (95% CI), %	−47 (−65 to −20)	...	−45 (−74 to −17)	...	−11 (−48 to 52)	...	12 (−46 to 126)	...	−11 (−52 to 65)	...
<85% Sao_2 threshold										
Time, mean (SD), s/h	19.4 (22.0)	46.2 (49.9)	21.0 (25.3)	46.1 (66.4)	26.6 (38.2)	28.7 (38.6)	33.5 (62.3)	27.2 (37.7)	17.0 (19.8)	17.2 (21.0)
Change (95% CI), %	−56 (−74 to −27)	...	−46 (−68 to −10)	...	−2 (−47 to 81)	...	34 (−43 to 312)	...	11 (−44 to 121)	...
<80% Sao_2 threshold										
Time, mean (SD), s/h	7.6 (10.8)	20.3 (27.9)	9.5 (12.6)	21.3 (36.9)	13.7 (22.7)	12.6 (19.7)	16.1 (31.3)	12.3 (21.5)	7.7 (9.2)	6.8 (11.0)
Change (95% CI), %	−64 (−81 to −32)	...	−45 (−70 to 0)	...	19 (−41 to 144)	...	46 (−44 to 281)	...	20 (−45 to 160)	...

Abbreviations: PMA, postmenstrual age; Sao_2, hemoglobin oxygen saturation.

[a] Estimated changes in caffeine treatment group relative to usual care (control) group and 95% CIs were determined from generalized estimating equation gamma regressions for longitudinal data.

Figure 2. Time Below 3 Different Hemoglobin Oxygen Saturation (Sao_2) Thresholds at 35 and 36 Weeks' Postmenstrual Age (PMA) at 3 Different Saturation Thresholds



Time (in seconds per hour) of Sao_2 at thresholds of less than 90%, less than 85%, and less than 80% are shown for the total cohort (n = 95) at 35 and 36 weeks' PMA. Although the total time was greater with a threshold of less than 90% or less than 85%, the magnitude of the decrease with caffeine is comparable for a threshold of less than 80% at both 35 and 36 weeks. *P < .01; †P < .05. With extended caffeine treatment, intermittent hypoxia at the less-than-80% threshold was decreased by 64% at 35 weeks' PMA (P = .002), but the 45% decrease at 36 weeks' PMA was only borderline significant (P = .051).

Our study extends observations from the only prior study of IH in the NICU using continuous oximeter recordings.[12] That study showed that IH episodes to ≤80% Sao_2 in infants born at less than 28 weeks' gestation were very frequent at a postnatal age of 4 to 8 weeks. Several studies have confirmed that symptomatic immature respiratory patterns and overt apnea-related associated bradycardia and desaturations can continue until term-equivalent age and even beyond, in particular for infants born at less than 28 weeks' gestation.[24,25] As we documented for the first time by using continuous oximeter recordings, repetitive, clinically inapparent and self-resolving IH is common and continues to be evident after resolution of overt clinical symptoms.

One prior randomized trial did not show a significant effect of caffeine on episodes of hypoxia, but that study used much less sensitive methods for identification of hypoxia, used different definitions of hypoxia, and recorded for much shorter durations.[26] In contrast, our study used a state-of-the-art motion-resistant oximeter with 2-second averaging and obtained weeks of continuous data to detect IH comprehensively, and we demonstrated significant reductions in IH at 35 and 36 weeks' PMA with extended caffeine treatment.

A critical but unresolved question is whether reducing the extent of IH by extending caffeine treatment to term-equivalent age has any long-term benefits, such as improved neurodevelopment, or any associated risks. Events associated with IH in early infancy, however, have been shown to have adverse effects on neurodevelopment at 1 year corrected age in infants born prematurely.[17] Furthermore, the adverse effect of IH on cognitive performance, including executive function, has been documented in children and adults with IH secondary to sleep-disordered breathing, even with a relatively modest extent of IH.[27-31]

Despite the lack of studies assessing the effects of extended caffeine treatment on later neurodevelopmental outcomes in preterm infants, there are clinical trial data on motor and cognitive neurodevelopmental outcomes associated with caffeine treatment during the acute illness treatment phase in the NICU, including at higher doses.[32] In the Caffeine for Apnea of Prematurity (CAP) trial, treatment with caffeine in the NICU reduced the likelihood of death, clinical disability, or neurocognitive impairment at 18 months' PMA.[33] At 5 years, there were significant improvements in visual perception and motor performance, including coordination.[22] Moreover, improvements in motor function in caffeine-exposed infants in the CAP trial were associated with improved cerebral white matter microstructural development seen with magnetic resonance imaging at term-equivalent age.[34] The CAP trial was not designed to delineate the mechanisms by which earlier caffeine treatment improved later neurodevelopment, and IH was not assessed. However, our study results suggest that one mechanism could be the improvement of central respiratory control, resulting in fewer symptoms related to apnea of prematurity, including IH.

Our study also confirmed that extended use of caffeine has a very favorable safety profile. Consistent with current clinical practice, all the infants in our study, regardless of the arm to which they were randomized, needed to be apnea free for a specified minimum duration before discharge. Our study focused on clinically inapparent hypoxia and not clinically apparent apnea, so our study does not yield any new insights regarding the effect of resolving apnea in discharge planning. Of note, only 1 infant in our entire study population required rehospitalization within 6 months after study completion, and this infant was from the control cohort.

The major strengths of our study include the use of an external data recorder to obtain and store long-term continuous recordings of Sao_2 and heart rate and a simple, validated, automated software-based analysis of these oximeter recordings.[23] Our automated scoring strategy was based on SIQ. This method excludes artifactual values and includes only desaturation episodes with an SIQ of more than 0.3 and no low perfusion tag within the 7-second signal processing time of the monitor. This approach has been demonstrated to show results comparable to those of analyses based on visual inspection of waveforms.[23] We also used a short (2-second) oximeter averaging time to record the frequent but typically brief IH episodes that continue to occur after routine clinical caffeine treatment is discontinued.[14,16,25] In the assessment of clinically inapparent hypoxia, shorter averaging times improve the detection of IH events and severe desaturations.[35]

Our study has several limitations. All infants in the caffeine group received a caffeine maintenance dosage of 6 mg/kg/d. This is a common dosage used at younger postnatal ages, but pharmacokinetic data suggest that this maintenance caffeine dosage may not be sufficient after 36 weeks owing to the increasing metabolism of caffeine.[36-39] Additional studies are needed to clarify why caffeine in our study had no significant effect on extent of IH after 36 weeks. However, preliminary results from a caffeine pharmacokinetic study in progress suggest that an insufficient maintenance dose of caffeine may explain our inability to demonstrate a continuing significant reduction in IH with caffeine after 36 weeks' PMA (unpublished data).

Despite the block randomization design, there was some imbalance in size between the 2 treatment groups. Randomizing all siblings from a multiple birth to the same treatment group probably contributed to this imbalance. The similarity in the demographic and clinical characteristics between the 2 treatment groups, however, should still permit meaningful statistical comparison, and it is not likely that the effect of caffeine in decreasing IH was affected. The inclusion of multiple infants from a family could bias the results owing to intrafamily correlation. To explore the effect of including twin and triplet siblings in our analyses, we repeated the analyses including only the firstborn infant from each set of twins or triplets. This approach is conservative in that it ignores data from other siblings. However, this analysis gave similar results in terms of both estimated effects and significance, supporting the findings of our primary analysis. Finally, we did not use a placebo for our study, and treatment group assignment was thus not masked. However, clinical management was equivalent in the caffeine and usual-care groups because the occurring IH was not associated with clinical symptoms, and analysis of the recorded pulse oximeter data—our primary outcome—was performed by study personnel masked to patient group. Finally, although there may be important insights to be gained from comparing infants born at a younger GA with those born at an older GA, our post hoc comparison of infants born before vs after 29.5 weeks had limited power to assess meaningful differences.

Conclusions

Clinically inapparent episodes of IH are frequent in preterm infants after discontinuation of routine clinical caffeine treatment in the NICU. Most important, extending caffeine treatment beyond current clinical indications significantly decreases the frequency and severity of IH at 35 and 36 weeks' PMA. Further studies are needed to (1) establish the dose of caffeine required to minimize the extent of IH, (2) determine whether optimal caffeine dosing results in a sustained significant reduction in IH at more than 36 weeks' PMA, and (3) assess the benefits and risks that may result

from extended caffeine treatment duration in very low-birth-weight infants. Pending results from such studies, the clinical importance of the IH observed in our study is unknown and therefore should not be the basis for changing current practices regarding the discharge planning of infants born prematurely.

ARTICLE INFORMATION

Accepted for Publication: September 10, 2013.

Published Online: January 20, 2014. doi:10.1001/jamapediatrics.2013.4371.

Author Affiliations: Newborn Medicine and Respiratory Diseases, Boston Children's Hospital, Boston, Massachusetts (Rhein); Department of Pediatrics, Uniformed Services University of Health Sciences, Bethesda, Maryland (Dobson, Hunt); Department of Pediatrics, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire (Darnall); Department of Pediatrics, Boston University School of Medicine, Boston, Massachusetts (Corwin); Slone Epidemiology Center at Boston University, Boston, Massachusetts (Corwin); Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts (Heeren); Department of Neonatology, University of Tübingen, Tübingen, Germany (Poets); American SIDS Institute, Naples, Florida (McEntire).

The Caffeine Pilot Study Group includes Henrietta Bada, MD; Wally Carlo, MD; Larry Consenstein, MD; Mary Lucia Gregory, MD; Karen Hendricks-Munoz, MD; Deborah Hoy, MD; Nilima Karamchandani, MD; Judith M. Klarr, MD; Praveen Kumar, MD; Corinne L. Leach, MD; Joan Richardson, MD; Ted S. Rosenkrantz, MD; Robert D. White, MD.

The Caffeine Pilot Study Group Affiliations: Department of Neonatology, Kentucky Children's Hospital, Lexington (Bada); Division of Neonatology, University of Alabama, Birmingham (Carlo); Department of Pediatrics, St Joseph's Hospital Health Center, Syracuse, New York (Consenstein); Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts (Gregory); Division of Neonatology, Department of Pediatrics, Bellevue Hospital, New York University, New York (Hendricks-Munoz); Department of Pediatrics, Georgetown University, Washington DC (Hoy); Department of Pediatrics, Western Pennsylvania Hospital, Pittsburgh (Karamchandani); Division of Neonatal-Perinatal Medicine, Department of Pediatrics, William Beaumont Hospital, Royal Oak, Michigan (Klarr); Department of Pediatrics, Northwestern Memorial Hospital, Northwestern University, Chicago, Illinois (Kumar); Department of Pediatrics, Women's and Children's Hospital of Buffalo, State University of New York at Buffalo (Leach); Division of Neonatology, Department of Pediatrics, University of Texas, Galveston (Richardson); Department of Pediatrics, University of Connecticut Health Center, Farmington (Rosenkrantz); Department of Pediatrics, Memorial Hospital, South Bend, Indiana (White).

Author Contributions: Drs Hunt and Corwin have 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.
Study concept and design: Rhein, Dobson, Darnall, Corwin, Poets, McEntire, Hunt, Carlo, Consenstein, Hendricks-Munoz, Hoy, Richardson.
Acquisition of data: Rhein, Dobson, Darnall, McEntire, Hunt, Bada, Consenstein, Gregory, Karamchandani, Klarr, Kumar, Leach, Rosenkrantz, White.
Analysis and interpretation of data: Rhein, Darnall, Corwin, Heeren, McEntire, Hunt, Consenstein.
Drafting of the manuscript: Rhein, Dobson, McEntire, Hunt, Hendricks-Munoz, Leach, Rosenkrantz.
Critical revision of the manuscript for important intellectual content: Rhein, Dobson, Darnall, Corwin, Heeren, Poets, McEntire, Hunt, Bada, Carlo, Consenstein, Gregory, Hoy, Karamchandani, Klarr, Kumar, Richardson, White.
Statistical analysis: Heeren.
Obtained funding: McEntire.
Administrative, technical, or material support: Poets, McEntire, Hunt, Carlo, Consenstein, Hendricks-Munoz, Kumar, Leach, Rosenkrantz.
Study supervision: Darnall, Corwin, McEntire, Hunt, Bada, Karamchandani, Klarr, Kumar, Rosenkrantz.

Conflict of Interest Disclosures: Dr McEntire reports being the executive director of the American SIDS Institute, and Dr Hunt reports being a member of the American SIDS Institute board of directors. No other disclosures were reported.

Funding/Support: This study was supported in part by the American SIDS Institute.

Role of the Sponsors: The funding source had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Army, Department of Defense, or the US government. Some authors are military service members or US government employees. This work was prepared as part of their official duties. Title 17 USC §105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 USC §101 defines US government work as work prepared by a military service member or employee of the US government as part of that person's official duties.

Previous Presentation: Presented in part at the Pediatric Academic Societies annual meeting; May 5, 2013; Washington, DC.

Additional Contributions: We thank Denis Rybin, MS, for his active participation in data analysis, including statistical analysis; Masimo Corporation for providing the pulse oximeters; and Acumen Instruments Corporation for providing the serial data recorders. Mr Rybin did not receive compensation for his work.

REFERENCES

1. Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. *Sleep*. 2009;32(2):150-157.

2. Urlesberger B, Kaspirek A, Pichler G, Müller W. Apnoea of prematurity and changes in cerebral oxygenation and cerebral blood volume. *Neuropediatrics*. 1999;30(1):29-33.

3. Poets CF. Apnea of prematurity: what can observational studies tell us about pathophysiology? *Sleep Med*. 2010;11(7):701-707.

4. Mathew OP. Apnea of prematurity: pathogenesis and management strategies. *J Perinatol*. 2011;31(5):302-310.

5. Nagata N, Saji M, Ito T, Ikeno S, Takahashi H, Terakawa N. Repetitive intermittent hypoxia-ischemia and brain damage in neonatal rats. *Brain Dev*. 2000;22(5):315-320.

6. Prabhakar NR. Oxygen sensing during intermittent hypoxia: cellular and molecular mechanisms. *J Appl Physiol (1985)*. 2001;90(5):1986-1994.

7. Feldman JL, Mitchell GS, Nattie EE. Breathing: rhythmicity, plasticity, chemosensitivity. *Annu Rev Neurosci*. 2003;26(1):239-266.

8. Douglas RM, Miyasaka N, Takahashi K, Latuszek-Barrantes A, Haddad GG, Hetherington HP. Chronic intermittent but not constant hypoxia decreases NAA/Cr ratios in neonatal mouse hippocampus and thalamus. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(3):R1254-R1259.

9. Machaalani R, Waters KA. Postnatal nicotine and/or intermittent hypercapnic hypoxia effects on apoptotic markers in the developing piglet brainstem medulla. *Neuroscience*. 2006;142(1):107-117.

10. Ratner V, Kishkurno SV, Slinko SK, et al. The contribution of intermittent hypoxemia to late neurological handicap in mice with hyperoxia-induced lung injury. *Neonatology*. 2007;92(1):50-58.

11. Ratner V, Slinko S, Utkina-Sosunova I, Starkov A, Polin RA, Ten VS. Hypoxic stress exacerbates hyperoxia-induced lung injury in a neonatal mouse model of bronchopulmonary dysplasia. *Neonatology*. 2009;95(4):299-305.

12. Di Fiore JM, Bloom JN, Orge F, et al. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr*. 2010;157(1):69-73.

13. Hunt CE, Corwin MJ, Weese-Mayer DE, et al; Collaborative Home Infant Monitoring Evaluation (CHIME) Study Group. Longitudinal assessment of hemoglobin oxygen saturation in preterm and term infants in the first six months of life. *J Pediatr*. 2011;159(3):377-383.

14. Poets CF, Stebbens VA, Alexander JR, Arrowsmith WA, Salfield SA, Southall DP. Arterial oxygen saturation in preterm infants at discharge from the hospital and six weeks later. *J Pediatr*. 1992;120(3):447-454.

15. Ramanathan R, Corwin MJ, Hunt CE, et al; Collaborative Home Infant Monitoring Evaluation (CHIME) Study Group. Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS. *JAMA*. 2001;285(17):2199-2207.

16. Côté A, Hum C, Brouillette RT, Themens M. Frequency and timing of recurrent events in infants using home cardiorespiratory monitors. *J Pediatr*. 1998;132(5):783-789.

17. Hunt CE, Corwin MJ, Baird T, et al; Collaborative Home Infant Monitoring Evaluation study group. Cardiorespiratory events detected by home

memory monitoring and one-year neurodevelopmental outcome. *J Pediatr*. 2004;145(4):465-471.

18. Pillekamp F, Hermann C, Keller T, von Gontard A, Kribs A, Roth B. Factors influencing apnea and bradycardia of prematurity: implications for neurodevelopment. *Neonatology*. 2007;91(3):155-161.

19. Heyman E, Ohlsson A, Heyman Z, Fong K. The effect of aminophylline on the excursions of the diaphragm in preterm neonates: a randomized double-blind controlled study. *Acta Paediatr Scand*. 1991;80(3):308-315.

20. Bauer J, Maier K, Linderkamp O, Hentschel R. Effect of caffeine on oxygen consumption and metabolic rate in very low birth weight infants with idiopathic apnea. *Pediatrics*. 2001;107(4):660-663.

21. Bhatt-Mehta V, Schumacher RE. Treatment of apnea of prematurity. *Paediatr Drugs*. 2003;5(3):195-210.

22. Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357(19):1893-1902.

23. Brockmann PE, Poets A, Urschitz MS, Sokollik C, Poets CF. Reference values for pulse oximetry recordings in healthy term neonates during their first 5 days of life. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(5):F335-F338.

24. Darnall RA, Kattwinkel J, Nattie C, Robinson M. Margin of safety for discharge after apnea in preterm infants. *Pediatrics*. 1997;100(5):795-801.

25. Eichenwald EC, Aina A, Stark AR. Apnea frequently persists beyond term gestation in infants delivered at 24 to 28 weeks. *Pediatrics*. 1997;100(3, pt 1):354-359.

26. Bucher HU, Duc G. Does caffeine prevent hypoxaemic episodes in premature infants? a randomized controlled trial. *Eur J Pediatr*. 1988;147(3):288-291.

27. Urschitz MS, Guenther A, Eggebrecht E, et al. Snoring, intermittent hypoxia and academic performance in primary school children. *Am J Respir Crit Care Med*. 2003;168(4):464-468.

28. Bass JL, Corwin M, Gozal D, et al. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. *Pediatrics*. 2004;114(3):805-816.

29. Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour and psychological functioning. *Eur J Pediatr*. 1996;155(1):56-62.

30. Kheirandish L, Gozal D, Pequignot JM, Pequignot J, Row BW. Intermittent hypoxia during development induces long-term alterations in spatial working memory, monoamines, and dendritic branching in rat frontal cortex. *Pediatr Res*. 2005;58(3):594-599.

31. Decker MJ, Hue GE, Caudle WM, Miller GW, Keating GL, Rye DB. Episodic neonatal hypoxia evokes executive dysfunction and regionally specific alterations in markers of dopamine signaling. *Neuroscience*. 2003;117(2):417-425.

32. Gray PH, Flenady VJ, Charles BG, Steer PA; Caffeine Collaborative Study Group. Caffeine citrate for very preterm infants: effects on development, temperament and behaviour. *J Paediatr Child Health*. 2011;47(4):167-172.

33. Schmidt B, Anderson PJ, Doyle LW, et al; Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA*. 2012;307(3):275-282.

34. Doyle LW, Cheong J, Hunt RW, et al. Caffeine and brain development in very preterm infants. *Ann Neurol*. 2010;68(5):734-742.

35. Ahmed SJM, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. *Pediatrics*. 2010;125(1):e115-e121.

36. Le Guennec JC, Billon B, Paré C. Maturational changes of caffeine concentrations and disposition in infancy during maintenance therapy for apnea of prematurity: influence of gestational age, hepatic disease, and breast-feeding. *Pediatrics*. 1985;76(5):834-840.

37. Carrier O, Pons G, Rey E, et al. Maturation of caffeine metabolic pathways in infancy. *Clin Pharmacol Ther*. 1988;44(2):145-151.

38. Thomson AH, Kerr S, Wright S. Population pharmacokinetics of caffeine in neonates and young infants. *Ther Drug Monit*. 1996;18(3):245-253.

39. Charles BG, Townsend SR, Steer PA, Flenady VJ, Gray PH, Shearman A. Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. *Ther Drug Monit*. 2008;30(6):709-716.