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Extended Caffeine for Apnea in Moderately Preterm Infants
The MoCHA Randomized Clinical Trial

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IMPORTANCE Hospitalization of moderately preterm infants may be prolonged while waiting for apnea of prematurity to resolve after discontinuing caffeine.

OBJECTIVE To evaluate whether extending caffeine treatment reduces the duration of hospitalization.

DESIGN, SETTING, AND PARTICIPANTS From February 2019 to December 2022, this randomized clinical trial in 29 US hospitals enrolled infants born at 29 to 33 weeks' gestation who at 33 to 35 weeks' postmenstrual age were receiving caffeine treatment with plans to discontinue it plus receiving full feeds (≥120 mL/kg/d). Follow-up was completed on March 20, 2023.

INTERVENTIONS Infants were randomized to oral caffeine citrate (10 mg/kg/d) or placebo until 28 days after discharge.

MAIN OUTCOMES AND MEASURES The primary outcome was days to discharge after randomization. Secondary outcomes included days to physiological maturity (apnea free for 5 consecutive days, receiving full oral feeds, and out of the incubator for at least 48 hours), postmenstrual age at discharge, all-cause hospital readmissions, all-cause sick and emergency department visits, safety outcomes, and death.

RESULTS A total of 827 infants (median gestational age, 31 weeks; 414 female [51%]) were randomized (416, caffeine; 411, placebo) out of the 878 planned before reaching the prespecified futility threshold. Days of hospitalization after randomization did not differ between groups (18.0 days [IQR, 10 to 30 days] for caffeine vs 16.5 [IQR, 10 to 27 days] for placebo; adjusted median difference, 0 days [95% CI, −1.7 to 1.7 days]), nor did days to physiological maturity differ (14.0 vs 15.0 days, adjusted median difference, −1 day [95% CI, −2.4 to 0.4 days]). Infants receiving caffeine were apnea free sooner (6.0 vs 10.0 days; adjusted median difference, −2.7 days [95% CI, −3.4 to −2.0 days]) but had similar days to full oral feeding (7.5 vs 6.0 days, adjusted median difference, 0 days [95% CI, −0.1 to 0.1]). Rates of readmissions and sick visits did not differ between groups. There was no statistically significant difference in adverse events between the 2 groups.

CONCLUSIONS AND RELEVANCE In moderately preterm infants, continuation of caffeine treatment compared with placebo did not shorten hospitalization.

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Visual Abstract

Supplemental content

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Apnea of prematurity is one of the most common disorders in moderately preterm infants,[1] and delayed resolution of apnea of prematurity and attainment of oral feeding are the most common factors prolonging hospitalization of moderately preterm infants.[2,3] Caffeine and other methylxanthines are highly effective in reducing apnea but can have adverse effects[4] and should not be continued longer than necessary. Evidence about the effectiveness and safety of extending caffeine therapy beyond initial apnea resolution in preterm infants is limited.[5] A meta-analysis published in 2024 (3 trials, 392 preterm infants) found limited data on the benefits and harms of different caffeine cessation strategies in preterm infants and called for further assessment of their short- and long-term effects.[6]

Because the optimal timing to discontinue caffeine in preterm infants is unknown, there is wide practice variation in the timing of discontinuation of caffeine. In a large cohort study of 81 110 infants younger than 35 weeks' gestational age from 304 neonatal intensive care units, caffeine discontinuation ranged from 32 to 37 weeks and late discontinuation was associated with earlier postmenstrual age (PMA) at the time of discharge.[7] In hospitals that discontinue caffeine before discharge, the usual practice is to observe infants for 5 to 10 days after discontinuing caffeine because therapeutic levels persist through that period and could mask immature respiratory control.[8] This potentially delays discharge.

In addition, preterm infants are at elevated risk of apnea after hospital discharge.[9] In theory, continuing caffeine through hospitalization and beyond discharge might reduce length of hospitalization, hospital readmissions, or sick visits due to suspected apnea of prematurity. However, evidence is unclear regarding the benefits and risks of extending caffeine after hospital discharge.

This trial was designed to test the hypothesis that in moderately preterm infants with planned discontinuation of caffeine, extending caffeine therapy until 28 days after discharge compared with placebo decreases the number of days from randomization to discharge. Secondary hypotheses assessed whether continuing caffeine after discharge decreases readmission to the hospital or sick visits to the emergency department, urgent care, or clinician's office.

Key Points

Question Can extended caffeine treatment reduce the duration of hospitalization while waiting for apnea of prematurity to resolve?

Findings In this randomized clinical trial of infants born at 29 to 33 weeks' gestation who were receiving caffeine at 33 to 35 weeks' postmenstrual age, those who continued to receive caffeine vs placebo had similar days of hospitalization after randomization (18.0 vs 16.5 days). Days to physiological maturity did not differ, although infants receiving extended caffeine became apnea-free sooner.

Meaning Compared with the placebo, extended caffeine treatment did not shorten hospitalization.

Methods

Study Design

The Moderately Preterm Infants with Caffeine at Home for Apnea (MoCHA) trial was a randomized, placebo-controlled trial with parallel enrollment and 1:1 allocation conducted in the 29 hospitals of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN). The study was approved by the institutional review boards at each participating center and at (Research Triangle Institute) RTI International. Written informed consent was obtained from a parent or guardian of each infant. Data were transmitted to RTI International, the data coordinating center, which stored, managed, and analyzed the data. The trial protocol and statistical analysis plan are available in Supplement 1 and their amendments in Supplement 2. The Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines were followed.

Patients

Infants born at 29 0/7 to 33 6/7 weeks' gestation were eligible for enrollment if they met all the following criteria: (1) being 33 0/7 to 35 6/7 weeks' PMA at the time of randomization; (2) receiving caffeine with plan to discontinue treatment; (3) receiving oral and/or tube feedings at 120 mL/kg/d or more; and (4) having the ability to start the study medication within 72 hours after stopping caffeine. Infants were excluded if they met any of the following criteria: (1) receiving respiratory therapy (ie, supplemental oxygen [more than room air equivalent for high altitude sites], nasal cannula, continuous positive airway pressure ventilation, and/or mechanical ventilation); (2) being discharged from an apnea monitor due to underlying disease or family history, including history of a sibling with sudden infant death syndrome; (3) parents requesting an apnea monitor; (4) having congenital heart disease other than atrial septal defect, ventricular septal defect, or patent ductus arteriosus; (5) having a neuromuscular condition affecting respiration; (6) having major congenital malformation and/or genetic disorder; or (7) planning to transfer to a non-NRN site before discharge. The race and ethnicity of the infants' mothers were self-reported and selected from a list of predetermined categories.

Enrollment and Randomization

Infants were randomized centrally with stratification by center and gestational age (29 0/7 to 30 6/7 weeks or 31 0/7 to 33 6/7 weeks). Infants of multiple births were randomized separately. Other than the study pharmacists, all research staff, health care staff, outcome assessors, and family members were masked to treatment allocation.

Intervention

Infants were randomized to continuing enteral caffeine citrate (10 mg/kg/dose, 5 mg/kg caffeine base) or an equal volume of placebo that contained all excipients except the caffeine citrate (Exela Pharma Sciences), administered daily and continued through the hospital stay and for 28 days after discharge.

The fixed number of days of treatment after discharge was chosen rather than treatment until a specified PMA because the resolution of apnea of prematurity varies greatly among infants. In-hospital dosages were weight-adjusted weekly. Following randomization, apnea events were assessed by the attending neonatologists using individualized management of possible apnea events with reliance on clinical monitoring documentation per local practice using apnea monitors. If the attending neonatologist decided that caffeine reinitiation was clinically indicated for apnea recurrence, open-label caffeine was allowed, and the study drug was put on hold until the open-label caffeine was discontinued. Infants receiving the study drug who remained in the hospital at 44 weeks PMA had the study drug discontinued.

Once the infant was deemed ready for discharge, the parent was supplied with 28 numbered vials of daily oral study drug dosed based on the infant's weight. Study medication could be administered at any time on the scheduled day if doses were given at least 12 hours apart. Parents were instructed to record the information on doses given on the data forms provided. Home apnea monitoring was not used.

A member of the research team contacted the parents to answer questions, assess medication adherence, and obtain post-discharge information within 72 hours after discharge and on weeks 1, 2, 3, 4, 6, and 8 after discharge. Data forms given to the parents to complete up to 8 weeks after discharge included the following fields: (1) daily item to mark if the medication was administered, (2) sick visits and hospitalizations, (3) weights obtained during well-child or sick visits, (4) missed doses of study medication, and (5) new medications prescribed.

Outcomes

The primary outcome was the number of days of hospitalization from randomization to discharge, which was defined as up to 48 weeks PMA with censoring at the time of transfer or death. Secondary outcomes included: the number of days to physiological maturity and for each of the following measures, which included being out of an incubator for at least 48 hours, managing oral feeding at volume of at least 140 mL/kg/d or gaining weight for at least 48 hours on fewer feeds, and being apnea free for at least 5 consecutive days; PMA at discharge; and the number of all-cause hospital readmissions and the number of all-cause sick visits to urgent care, emergency department, or clinician's office within the first 4 weeks, second 4 weeks, and first 8 weeks after discharge up to 48 weeks' PMA. Prespecified, serious adverse events included arrhythmias (excluding tachycardia or bradycardia), seizures, hospitalization, and death. Safety measures included tachycardia, defined as at least 2 consecutive heart rates of more than 200 beats per minute documented at least 3 hours apart; sick visit to urgent care, emergency department, or clinician's office related to apneic or brief resolved unexplained events; weight gain from randomization through discharge day and weight at status (status was defined status at discharge, transfer, or still in hospital at 48 weeks' PMA); treatment for high blood pressure; nothing by mouth for more than 24 hours; prescription of antireflux medication; and the number of days with significant apnea, as defined by documentation of receipt of any of the following between randomization and discharge: open-label caffeine, other methylxanthines, continuous positive airway pressure, or ventilatory support for apnea or bradycardia. Additional adverse events not prespecified but reported to be possibly related were analyzed also as adverse events including those classified as serious adverse events per US Food and Drug Administration (FDA) guidelines.[10]

Statistical Considerations

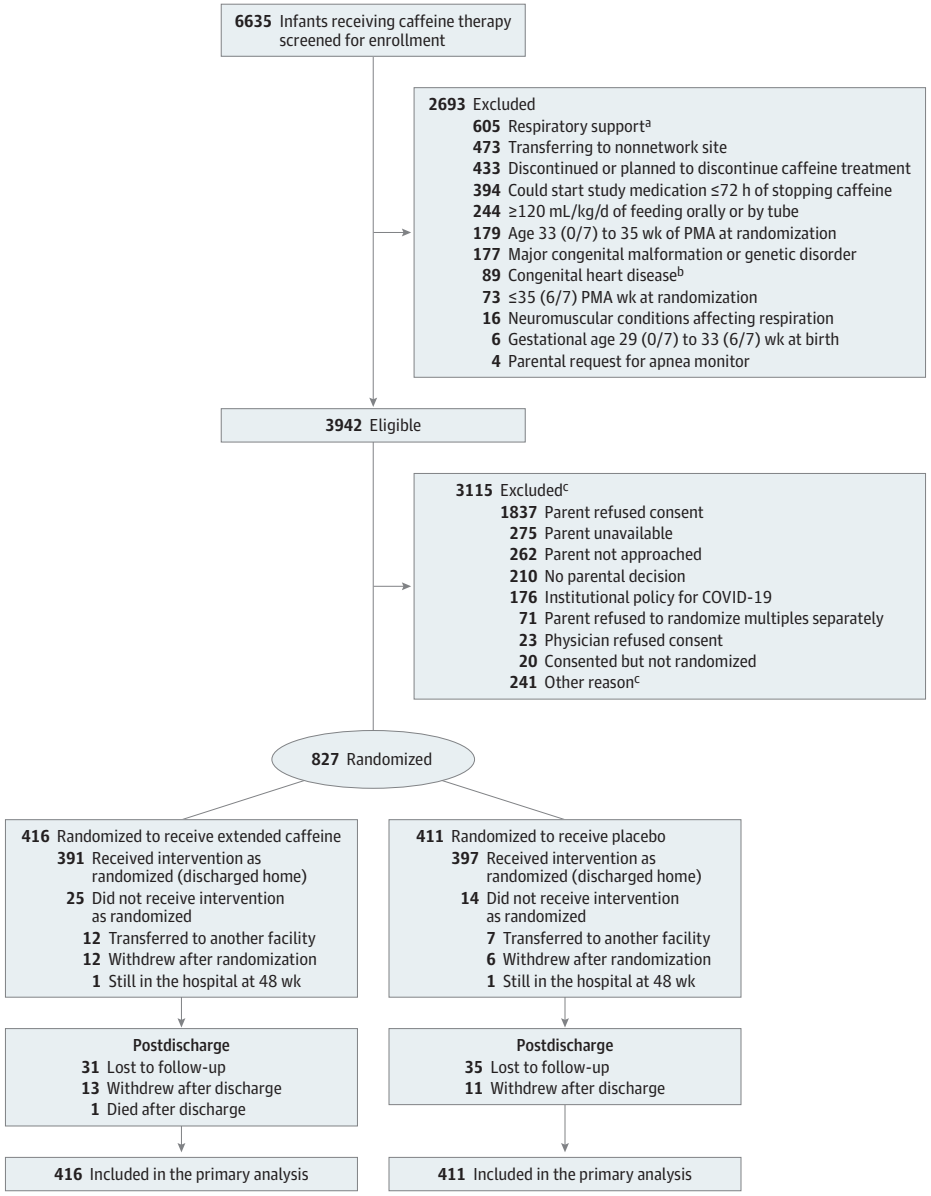
To detect a 2-day median reduction in primary outcome of days from randomization to discharge (from 14 to 12 days), with 90% power, significance of .05, and 5% attrition, the trial required 587 infants per group (intervention and placebo) for a total of 1174 infants, assuming a 2-tailed nonparametric test. For 80% power under the same scenario, the trial required 439 infants per group for a total of 878 infants. During the trial, the targeted power was changed from 90% to 80% with concurrence from the independent data and safety monitoring committee (DSMC) because the study drug expiration date together with the pause in recruitment due to COVID-19 precluded reaching full enrollment based on 90% power.

The primary analysis compared the number of days of hospitalization from randomization to discharge between the intervention and control groups, with censoring at death, transfer, or 48 weeks' PMA, whichever occurred first, using median regression with censoring, controlling for study center and gestational age group. The outcomes presented are based on the median regression, but we assessed it at censoring in the median time to event (survival analysis). The treatment effect for the secondary outcomes (number of days to physiological maturity after randomization, number of readmissions, and number of sick visits) was compared between groups using either median regression or a Poisson regression model controlling for study center and gestational age group. Secondary analysis evaluated whether other models better fitted the distributions for these outcomes (for example, survival analysis models for the primary outcome and negative binomial or log linear models for the secondary outcomes). This study examined treatment heterogeneity for the primary outcome by adding interaction terms between treatment and study center as well as between treatment and gestational age group and sex.

Analyses were performed according to the intention-to-treat principle. The denominator for each outcome rate was the number of infants with known outcomes. All analyses were conducted at RTI International. Two-sided P values <.05 were considered statistically significant. Analyses of secondary outcomes were only used for generating hypotheses and did not include adjustment for multiple comparisons. Subgroup analyses were conducted within prespecified gestational age strata for predefined outcomes.

The DSMC reviewed the primary outcome, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. Interim futility monitoring using conditional

Figure. Flow of Patients in the Moderately Preterm Infants Discharged With Caffeine at Home for Apnea (MoCHA) Trial



[a]Including oxygen, nasal cannula, continuous positive pressure ventilation, and/or mechanical ventilation.

[b]Excluding atrial septal defect, ventricular septal defect, or patent ductus arteriosus.

[c]Reasons for not randomizing eligible infants were selected from a predetermined set of likely reasons. Other reasons were uncategorized free text.

PMA indicates postmenstrual age.

power was conducted after 50% and 75% of the infants enrolled into the trial completed the 8-week follow up period.

Results

Infants were enrolled from February 2019 to December 2022, with a hospital-specific suspension of enrollment due to the COVID-19 pandemic during parts of 2020-2021. Enrollment was stopped early when 827 infants had been randomized (416 caffeine, 411 placebo) upon recommendation of the DSMC because of reaching a prespecified futility threshold of less than 15% conditional power to detect a statistically significant effect. Details on the eligibility, randomization, hospital discharge, and completion of the study are included in the **Figure.** Maternal and neonatal demographic and baseline characteristics did not differ between the groups (**Table 1**).

The number of days of hospitalization from randomization to discharge did not differ between the caffeine and the placebo groups (18.0 vs 16.5 days, IQR, 10 to 30; adjusted difference in medians, 0 days; 95% CI, −1.7 to 1.7; $P > .99$; **Table 2**; eFigure 1 in Supplement 3), nor did the number of days to physiological maturity (14.0 vs 15.0 days, adjusted difference in medians, −1 day; 95% CI, −2.4 to 0.4; for both groups; Table 2 and eFigure 2 in Supplement 3). Infants in the caffeine group were apnea free sooner (6.0 vs 10.0 days, adjusted difference in medians, −2.7 days; 95% CI, −3.4 to −2.0; eFigure 3 in Supplement 3). In post hoc analyses, fewer infants in the caffeine

Table 1. Summary of Demographics and Baseline Characteristics

Characteristic	Extended caffeine (n = 416)	Placebo (n = 411)
Maternal characteristics		
Mother's age, median (IQR), y	30.0 (26.0-34.0)	30.0 (26.0-34.0)
Mother's race, No. (%)[a]	401	398
American Indian or Alaska Native	7 (1.7)	12 (3.0)
Asian	12 (3.0)	9 (2.3)
Black	110 (27.4)	110 (27.6)
Native Hawaiian or Pacific Islander	4 (1.0)	4 (1.0)
White	265 (66.1)	261 (65.6)
≥1 Race	3 (0.7)	2 (0.5)
Mother's ethnicity, No. (%)	401	399
Hispanic or Latino	63 (15.7)	54 (13.5)
Not Hispanic or Latino	338 (84.3)	345 (86.5)
Marital status, No. (%)	413	408
Married	213 (51.6)	233 (57.1)
Single	200 (48.4)	175 (42.9)
Mother's education, No. (%)	337	342
Did not finish high school	42 (12.5)	27 (7.9)
Finished high school	86 (25.5)	102 (29.8)
Some post-high school education	209 (62.0)	213 (62.3)
Mother's medical insurance, No. (%)	416	410
Private	207 (49.8)	213 (52.0)
Public	203 (48.8)	190 (46.3)
Self-pay/uninsured	6 (1.4)	7 (1.7)
Gravidity, median (IQR), No.	2.5 (1.0-4.0)	2.0 (1.0-4.0)
Parity, median (IQR), No.	2.0 (1.0-3.0)	2.0 (1.0-3.0)
Child characteristics		
Sex, No. (%)	416	411
Female	213 (51.2)	207 (50.4)
Male	203 (48.8)	204 (49.6)
Gestational age, median (IQR), wk	31.1 (30.3-32.1)	31.1 (30.1-32.1)
Birth weight, median (IQR), g	1507.5 (1297.5-1750.0)	1580.0 (1304.0-1794.0)
Apgar score - 1 min, median (IQR)[b]	6 (4-8)	6 (4-8)
Apgar score - 5 min, median (IQR)[b]	8 (7-9)	8 (7-9)
Child interventions, No./total ((%)[c]		
Oxygen	344/415 (82.9)	342/410 (83.4)
CPAP	335/416 (80.5)	329/410 (80.2)
Positive pressure ventilation	228/416 (54.8)	225/410 (54.9)
Intubation	46/416 (11.1)	45/411 (10.9)
Chest compression	0/416 (0)	5/410 (1.2)
Epinephrine	0/416 (0)	2/411 (0.5)
Child characteristics at randomization, median (IQR)		
Postmenstrual age at randomization, wk	34.5 (34.1-35.3)	34.4 (34.1-35.3)
Randomization weight, g	1945.0 (1745.0-2190.0)	1950.0 (1770.0-2200.0)

Abbreviation: CPAP, continuous positive airway pressure.

[a] Race and ethnicity are self-reported by the infant's mother, selected among predetermined categories.

[b] Apgar score is an overall assessment of an infant's health status at birth. It ranges from 0 to 10 with high scores indicating a healthier infant.

[c] Treatments used at any time before randomization but not ongoing at the time of randomization.

group had significant apnea after randomization (4 of 414 [1.0%] vs 18 of 410 [4.4%], adjusted relative risk [RR], 0.22; 95% CI, 0.07 to 0.65; Table 2), and 2 infants (0.5%) in the caffeine group and 16 (3.9%) in the placebo group received open-label caffeine after randomization. The number of days out of the incubator for 48 hours (eFigure 4 in Supplement 3) and attainment of oral feeds of 140 mL/kg/d or more (Table 2; eFigure 5 in Supplement 3) or gaining weight while consuming less than 140 mL/kg/d for at least 48 hours (Table 2; eFigure 6 in Supplement 3) did not differ between the groups. The mean weight gain from randomization until discharge was lower in the caffeine group by 3 g/kg/d (95% CI, −5 to −2 g/kg/d). Tachycardia occurred more often in the caffeine group (adjusted RR, 2.43; 95% CI, 1.34 to 4.25). There was no statistically significant

Table 2. Summary of In-Hospital Outcomes After Randomization

Characteristic	Extended caffeine (n = 416)	Placebo (n = 411)	Model estimates	
			Difference in medians, means, or risk (95% CI)	Relative risk (95% CI)
Primary outcome				
No. of days of hospitalization, median (IQR)[a]	18.0 (10.0 to 30.0)	16.5 (10.0 to 27.0)	0 (−1.7 to 1.7)	NA
Secondary outcomes				
No. of days, median (IQR)				
To physiological maturity[a]	14.0 (7.0 to 24.0)	15.0 (8.0 to 24.0)	−1 (−2.4 to 0.4)	NA
To apnea or bradycardia free for 5 consecutive d[a]	6.0 (5.0 to 15.5)	10.0 (5.0 to 18.0)	−2.7 (−3.4 to −2.0)	NA
To release from incubator for 48 h continuous[a]	2.0 (2.0 to 5.0)	2.0 (2.0 to 5.0)	0 (0 to 0)	NA
To >140 mL/kg/d oral feeds or growing on <140 mL/kg/d ≤48 h[a]	7.5 (2.0 to 20.0)	6.0 (2.0 to 17.0)	0 (−0.1 to 0.1)	NA
All-cause mortality, No./total (%)[b]	1/416 (0.2)	0/411 (0.0)		
Postmenstrual age at discharge, mean (SD), wk[c]	37.7 (2.2)	37.6 (2.0)	0.2 (−0.1 to 0.4)	NA
In-hospital adverse events of concern, No. (%)				
Arrhythmia	1/414 (<1)	0/411		NA
Seizures	0/414	1/411 (<1)		NA
Death	0/414	0/411		NA
Other in-hospital outcomes				
Weight at status, mean (SD), g[c,d]	2584.9 (544.4)	2659.1 (602.0)	−74 (−148 to −1)	NA
Weight change from randomization until status, mean (SD), g/d[c,d]	28.9 (8.7)	32.2 (12.8)	−3 (−5 to −2)	NA
Tachycardia >200/min, No./total (%)[b]	35/414 (8.5)	15/411 (3.6)	4.85 (1.7 to 7.99)	2.43 (1.34 to 4.25)
Use of antireflux medications, No./total (%)[b]	30/414 (7.2)	24/411 (5.8)	1.34 (−1.91 to 4.59)	1.25 (0.73 to 2.1)
Significant apnea or bradycardia after randomization, No./total (%)[b]	4/414 (1.0)	18/410 (4.4)	−3.37 (−5.53 to −1.21)	0.22 (0.07 to 0.65)
NPO for ≥24 h, No./total (%)[b]	6/414 (1.4)	14/411 (3.4)	−1.94 (−4.00 to 0.12)	0.42 (0.16 to 1.08)
Treatment for high blood pressure, No./total (%)[b]	2/414 (0.5)	1/411 (0.2)		2.2 (0.19 to 24.4)

Abbreviations: blank cells, not able to estimate; NA, not applicable; NPO, nothing by mouth.

[a] Number of days outcomes were model using median regression and adjusted for the stratification factors of gestational age group and clinical center.

[b] Binary outcomes were modeled using logistic regression adjusted for the stratification factors of gestational age group and clinical center.

[c] Weight and age variables were modeled using general linear models adjusted for the stratification factors of gestational age group and clinical center.

[d] Status was the in-hospital status at discharge, transfer, or still in hospital at 48 weeks' postmenstral age.

difference in the number of adverse events between the 2 groups (**Table 3**).

All-cause hospital readmissions; all-cause sick visits, urgent care, emergency department, or clinician's office visits; and sick visits related to apnea or a brief, resolved unexplained event did not differ between the groups (**Table 4**; eTable 1 and eTable 2 in the Supplement 3). Weight change from randomization until 8 weeks after discharge did not differ between the groups (eFigure 6 in Supplement 3). The mean (SD) percentage of doses administered after discharge were 79.5% (2.9%) in the caffeine group and 87.6% (2.4%) in the placebo group ($P < .001$). Adherence with dose administration did not differ at any of the 5 times it was assessed during the 28-day period at home, but outliers accounted for the lower overall percentage adherence in the caffeine group (eFigure 7 in Supplement).

Discussion

This randomized placebo-controlled trial found that caffeine did not reduce the days of hospitalization from randomization to hospital discharge. Strengths of this trial included the large sample size and multicenter design, the important clinical outcomes assessed, and the masking to treatment assignment.

Days out of the incubator, days to full oral feeds, and days to physiological maturity did not differ between the groups. Although infants in the caffeine group had fewer days to becoming apnea free, the age at attainment of full oral feeding exceeded the age at resolution of apnea. Thus, caffeine continuation may not have reduced hospitalization days in moderately preterm infants because achievement of full oral feeds delayed discharge more often than apnea resolution.[11,12]

Table 3. Summary of Not Prespecified but Reported Adverse Events

Adverse event	No. (%) of infants		
	Extended caffeine	Placebo	Total
In-hospital			
No.	416	411	827
Necrotizing enterocolitis neonatal	0	4 (1)	4 (<1)
Hematochezia	0	1 (<1)	1 (<1)
Ileal stenosis	0	1 (<1)	1 (<1)
Mastoiditis	0	1 (<1)	1 (<1)
Neonatal tachycardia	0	1 (<1)	1 (<1)
Pyloric stenosis	1 (<1)	0	1 (<1)
Rhinovirus infection	0	1 (<1)	1 (<1)
Subperiosteal abscess	0	1 (<1)	1 (<1)
Any	11 (3)	21 (5)	32 (4)
Serious	2 (<1)	8 (2)	10 (1)
Postdischarge			
No.	390	397	787
Vomiting	0	4 (1)	4 (1)
Bronchiolitis	1 (<1)	2 (1)	3 (<1)
Respiratory syncytial virus infection	2 (1)	1 (<1)	3 (<1)
Enterovirus infection	1 (<1)	1 (<1)	2 (<1)
Influenza	1 (<1)	1 (<1)	2 (<1)
Rhinovirus infection	1 (<1)	1 (<1)	2 (<1)
Constipation	1 (<1)	0	1 (<1)
Cyanosis neonatal	0	1 (<1)	1 (<1)
Dehydration	0	1 (<1)	1 (<1)
Failure to thrive	1 (<1)	0	1 (<1)
Gastroesophageal reflux disease	0	1 (<1)	1 (<1)
Meningitis neonatal	0	1 (<1)	1 (<1)
Necrotizing enterocolitis neonatal	0	1 (<1)	1 (<1)
Neonatal hypoxia	0	1 (<1)	1 (<1)
Neonatal respiratory distress syndrome	1 (<1)	0	1 (<1)
Pneumonia moraxella	1 (<1)	0	1 (<1)
Road traffic crash	1 (<1)	0	1 (<1)
Seizure	1 (<1)	0	1 (<1)
Upper respiratory tract infection	0	1 (<1)	1 (<1)
Urinary tract infection neonatal	0	1 (<1)	1 (<1)
Any	12 (3)	18 (5)	30 (4)
Serious	8 (2)	12 (3)	20 (3)
In-hospital and postdischarge			
No.	416	411	827
Vomiting	0	4 (1)	4 (<1)
Bronchiolitis	1 (<1)	2 (<1)	3 (<1)
Respiratory syncytial virus infection	2 (<1)	1 (<1)	3 (<1)
Enterovirus infection	1 (<1)	1 (<1)	2 (<1)
Influenza	1 (<1)	1 (<1)	2 (<1)
Rhinovirus infection	1 (<1)	1 (<1)	2 (<1)
Constipation	1 (<1)	0	1 (<1)
Cyanosis neonatal	0	1 (<1)	1 (<1)
Dehydration	0	1 (<1)	1 (<1)
Failure to thrive	1 (<1)	0	1 (<1)
Gastroesophageal reflux disease	0	1 (<1)	1 (<1)
Meningitis neonatal	0	1 (<1)	1 (<1)

(continued)

Table 3. Summary of Not Prespecified but Reported Adverse Events (continued)

Adverse event	No. (%) of infants		
	Extended caffeine	Placebo	Total
Necrotizing enterocolitis neonatal	0	1 (<1)	1 (<1)
Neonatal hypoxia	0	1 (<1)	1 (<1)
Neonatal respiratory distress syndrome	1 (<1)	0	1 (<1)
Pneumonia moraxella	1 (<1)	0	1 (<1)
Road traffic crash	1 (<1)	0	1 (<1)
Seizure	1 (<1)	0	1 (<1)
Upper respiratory tract infection	0	1 (<1)	1 (<1)
Urinary tract infection neonatal	0	1 (<1)	1 (<1)
Any	19 (5)	31 (8)	50 (6)
Serious	10 (2)	18 (4)	28 (3)

Table 4. Summary of Postdischarge Outcomes

Postdischarge outcome	Extended caffeine (n = 390)		Placebo (n = 397)		Model estimated	
	No. of events	No. (%) of infants	No of events	No. (%) of infants	Difference in risk (95% CI)	Relative risk (95% CI)
Any all-cause readmissions[a]	27	24 (6)	30	25 (6)	−0.16 (−3.49 to 3.18)	0.97 (0.56 to 1.67)
Any all-cause sick visits, urgent care, emergency departments, or clinician's office[a]	126	89 (23)	106	77 (19)	3.38 (−2.26 to 9.01)	1.18 (0.89 to 1.52)
Any sick visits related to apneic or apparent life-threatening events[a]	32	22 (6)	37	29 (7)	−1.67 (−5.07 to 1.73)	0.77 (0.44 to 1.31)
		Mean (SD)		Mean (SD)	Model-estimated difference in means (95% CI)	
Weight change from randomization until 8 wks after discharge, g/d[b]		26.9 (6.2)		26.7 (8.1)	−2 (−4 to 1)	

[a] Binary outcomes were modeled using logistic regression adjusted for the stratification factors of gestational age group and clinical center.

[b] Weight change was modeled using a general linear model adjusted for the stratification factors of gestational age group and clinical center.

A potential weakness of the tested intervention was that the dose of caffeine citrate was 10 mg/kg/d. This is within the standard FDA recommended dose; however, this dose may be less effective than a higher dose. In a recent meta-analysis, a dose of 20 mg/kg/d was more effective for apnea reduction,[13] The higher dose may be preferable, especially at PMAs approaching term, due to the increased elimination of caffeine.[11,14]

The current trial's finding that infants receiving caffeine became apnea free 2 days sooner than those receiving placebo is consistent with 3 past multicenter randomized clinical trials of caffeine treatment around the time of discharge to home.[15-17] In these trials that included 259 preterm infants, continued caffeine beyond 34 to 37 weeks' PMA decreased intermittent hypoxemic events.[15-17] The current trial found earlier achievement of apnea-free status in the caffeine group, which is consistent with the results of these trials, because apnea and intermittent hypoxemic events frequently occur concurrently.

This trial represents an advance over past studies that were not powered to assess clinical outcomes and provides strong evidence to compare the clinical outcomes of infants discharged home receiving caffeine with those receiving placebo. In recent observational studies,[8,18,19] infants were discharged while receiving caffeine, but robust inferences about potential clinical benefits could not be made. Although there have been concerns of caffeine treatment causing adverse effects including gastrointestinal ones,[20] there was not a statistically significant difference in the number of adverse events reported between the 2 groups (Table 3). The tachycardia and initial lower mean weight gain in the caffeine group were transient.

Limitations

This study has several limitations. First, the treating physicians were allowed to use individualized management of possible apnea events, and the study relied on clinical documentation for assessment of apnea-free duration. However, treating physicians masked to treatment allocation made decisions regarding resolution of apnea events and achieving other measures of physiological maturity, which allowed rigorous and unbiased assessment of the clinical effects of caffeine. Second, another limitation was that a lower percentage of the doses planned were given in the caffeine group. Third, analyses of secondary outcomes were only used for generating hypotheses and did not include adjustment for multiple comparisons. Fourth, the relatively low follow-up rate was in part due to the COVID-19 pandemic but would not affect the hospital outcomes. Fifth, infants born at less than 29 weeks' gestational age who are at high risk of apnea of prematurity were not the target of this trial and were excluded because they are at a higher risk of other, higher morbidities that could confound the intervention.

Conclusions

In conclusion, this trial found that in moderately preterm infants with planned discontinuation of caffeine, continuation of caffeine until 28 days after discharge or 44 weeks' PMA did not reduce hospital days, hospital readmissions, or sick visits. Caffeine reduced days to resolution of apnea, but achievement of full oral feeds delayed discharge more than apnea resolution.

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Group Information: Members of for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network are listed in Supplement 4.

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