Early Caffeine and Weaning from Mechanical Ventilation in Preterm Infants: A Randomized, Placebo-Controlled Trial

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Objective To evaluate in a randomized, double-blind, placebo-controlled trial the effect of early caffeine on the age of first successful extubation in preterm infants.

Study design Preterm infants born at 23-30 weeks of gestation requiring mechanical ventilation in the first 5 postnatal days were randomized to receive a 20 mg/kg loading dose followed by 5 mg/kg/day of caffeine or placebo until considered ready for extubation. The placebo group received a blinded loading dose of caffeine before extubation.

Results Infants were randomized to receive caffeine (n = 41) or placebo (n = 42). Age at first successful extubation did not differ between early caffeine (median, 24 days; IQR, 10-41 days) and control groups (median, 20 days; IQR, 9-43 days; $P = .7$). An interim analysis at 75% enrollment showed a trend toward higher mortality in 1 of the groups and the data safety and monitoring board recommended stopping the trial. Unblinded analysis revealed mortality did not differ significantly between the early caffeine (9 [22%]) and control groups (5 [12%]; $P = .22$).

Conclusions Early initiation of caffeine in this group of premature infants did not reduce the age of first successful extubation. A nonsignificant trend toward higher mortality in the early caffeine group led to a cautious decision to stop the trial. These findings suggest caution with early use of caffeine in mechanically ventilated preterm infants until more efficacy and safety data become available. *(J Pediatr 2018;■■:■■-■■).*

Trial Registration ClinicalTrials.gov NCT01751724.

A large proportion of extreme premature infants require prolonged mechanical ventilation. This is associated with increased risk for bronchopulmonary dysplasia (BPD) and poor neurodevelopmental outcome.[1]

Caffeine, a methylxanthine and adenosine receptor antagonist, is a potent stimulant of central respiratory activity and is an effective treatment of apnea of prematurity and to avoid extubation failure.[2,3] However, adenosine has been shown to preserve brain cell survival and prevent brain energy failure by preserving adenosine triphosphate levels in experimental hypoxia and ischemia models.[4-6] Although caffeine has been used for these indications for the last 3 decades, until recently there were no long-term safety data to support its use.[7] The large, randomized, controlled trial, Caffeine for Apnea of Prematurity, showed that caffeine started for these indications within the first 10 days after birth did not have long-term negative effects on neurologic outcome or survival.[8,9] Analysis of predischarge outcomes showed a shorter duration of mechanical ventilation and a lower incidence of BPD in the caffeine compared with the placebo group. A secondary analysis showed that infants started on caffeine in the first 3 days while receiving mechanical ventilation derived the most benefit in terms of BPD and neurodevelopment.[10] Since then, the use of caffeine has increased and often is started earlier in mechanically ventilated preterm infants.[11]

Strategies to provide mechanical respiratory support have changed from controlled ventilation to a more gentle support, where the ventilator is used to assist the infant's spontaneous breathing. This step has been achieved in large part through the use of patient-triggered modes of mechanical ventilation. The effective use of these modes to reduce the need for mechanical ventilation must rely on the spontaneous respiratory drive, but this drive is frequently inconsistent in extremely premature infants. Thus, the use of respiratory stimulants such as caffeine seems to be a good alternative to decrease the duration of mechanical ventilation in this population. The efficacy and safety of this approach have not been evaluated by prospective, randomized, controlled trials.

We postulated that early initiation of caffeine in mechanically ventilated preterm infants will hasten the weaning process during the first course of mechanical ventilation. The primary objective of this trial was to evaluate the effect of early caffeine administration on the age of first successful extubation in mechanically

BPD	Bronchopulmonary dysplasia
DSMB	Data safety and monitoring board
FiO_2	Fraction of inspired oxygen
NICU	Neonatal intensive care unit

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ventilated preterm infants. The secondary objective was to evaluate the effect of early caffeine on total duration of mechanical ventilation and oxygen supplementation and on the incidence of BPD.

Methods

This single-center, double-blind, placebo-controlled, randomized clinical trial (ClinicalTrials.gov: NCT01751724) was conducted in the neonatal intensive care unit (NICU) at Holtz Children's Hospital of the Jackson Health System—University of Miami Medical Center.

Premature infants born between 23 and 30 weeks of gestation who required mechanical ventilation in the first 5 postnatal days were eligible for the study. Infants with major congenital anomalies and infants that were small for gestational age (birth weight <3rd percentile) were excluded.

Endpoints

The primary endpoint of the trial was the age of first successful extubation, defined as postnatal age of first extubation after which the infant remained extubated for >24 hours.

Secondary respiratory endpoints included total duration of mechanical ventilation, duration of oxygen supplementation, and the incidence of BPD. An oxygen or ventilator day was defined as the need for oxygen or mechanical ventilation for ≥12 hours over a 24-hour period. BPD was defined as need for supplemental oxygen for ≥28 days and at 36 weeks postmenstrual age. Severe BPD was defined as need for supplemental oxygen for ≥28 days and fraction of inspired oxygen (FiO_2) of ≥0.30 and/or positive pressure respiratory support at 36 weeks postmenstrual age.

Neonatal morbidities including pulmonary hemorrhage, echocardiography-confirmed patent ductus arteriosus, necrotizing enterocolitis defined as Bell's stage II or III, spontaneous intestinal perforation, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, and retinopathy of prematurity stage 3 or 4 were documented.

Interventions

After screening and enrollment with parental consent during the first 5 days after birth, mechanically ventilated infants were randomized to the early caffeine or control group (**Figure 1**). Randomization was stratified according to gestational age, either 23-26 or 27-30 weeks, using sealed, opaque envelopes. Stratification was aimed at balancing the number of infants within each gestational age bracket. Randomization and study drug preparation were done by the NICU pharmacy staff. Knowl-

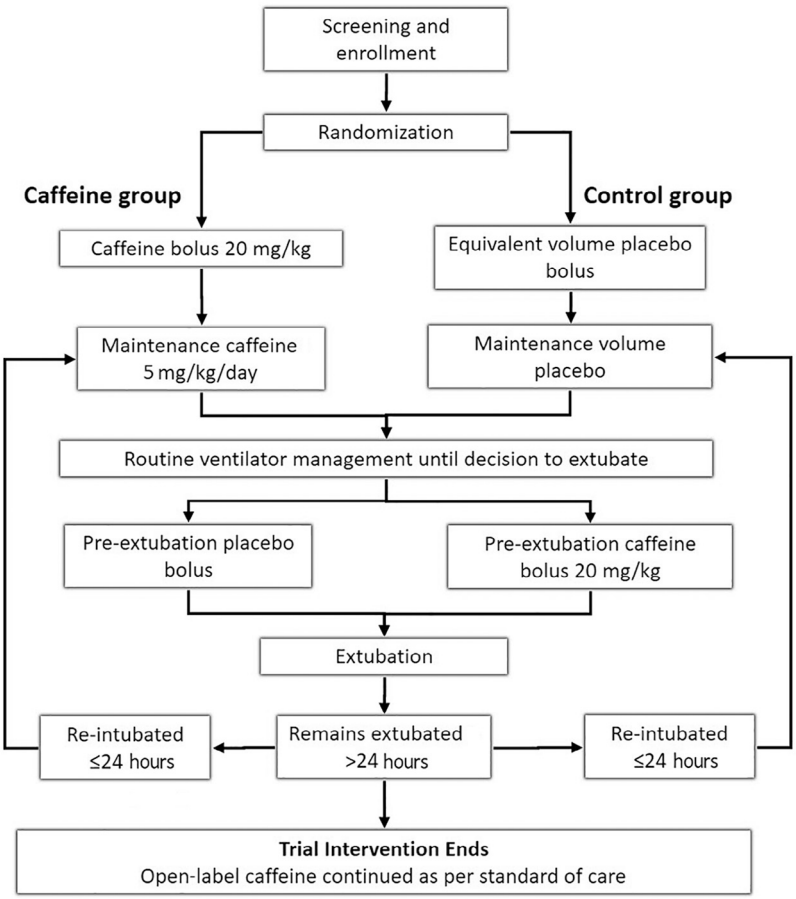

Figure 1. Trial flow diagram. Study protocol from screening to the end of the intervention.

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