Timing of Caffeine Therapy in Very Low Birth Weight Infants

Caffeine and other methylxanthines have been prescribed to treat apnea of prematurity for the past 40 years. However, for much of this time, the safety of the routine use of methylxanthines in preterm infants remained uncertain. Experimental evidence of potential harm was accumulating in the absence of rigorous evaluations of the effects of this drug therapy on clinically important outcomes of preterm infants. The international Caffeine for Apnea of Prematurity (CAP) trial was designed to end this long-standing therapeutic uncertainty. The CAP trial investigators enrolled more than 2000 infants with birth weights between 500 and 1250 g who were considered by their clinicians to be candidates for methylxanthine therapy during the first 10 days of life. Eligible infants were randomly assigned to receive either caffeine or placebo and followed to a corrected age of 5 years.

Neonatal caffeine therapy was found to reduce the risks of important short-term morbidities such as bronchopulmonary dysplasia (BPD) and severe retinopathy of prematurity, decrease the incidence of cerebral palsy and cognitive delay at 18 months, and improve gross motor function at 5 years. Nearly one-half of the neuroprotective effect of caffeine at 18 months could be explained by the earlier discontinuation of positive airway pressure in infants assigned to caffeine. Of all the neonatal treatments that have been subjected to economic evaluations, caffeine therapy is the most certain to be both cost-saving and beneficial. Caffeine has become the most frequently used medication after ampicillin and gentamicin in neonatal intensive care units in the US.

The CAP trial had broad and pragmatic eligibility criteria. A post hoc subgroup analysis examined whether the benefits of caffeine varied according to the indication for starting study medication, the level of respiratory support at randomization, and the postnatal age at initiation of study drug. The reasons for considering the CAP trial participants to be candidates for methylxanthine therapy were documented at their entry into the study and categorized as prevention of apnea, treatment of apnea, or facilitation of extubation. The beneficial effect of caffeine was consistent across these subgroups for all outcomes examined, including BPD. The level of respiratory support at randomization was recorded as no support, noninvasive respiratory support, or mechanical ventilation. This subgroup analysis raised the hypothesis that infants receiving respiratory support may derive greater benefit from caffeine than those not receiving support. The median age of starting study medication in the CAP trial was 3 days. Infants whose treatment with caffeine commenced at or before three days of age appeared to experience a greater reduction in the duration of respiratory support than those commencing treatment between 4 and 10 days of age.

In this issue of The Journal, Dobson et al compare the effect of early initiation of caffeine therapy at less than 3 days of life with later initiation of therapy in very low birth weight (VLBW) infants during the years 1997 to 2010. Using a large administrative database from the Pediatric Medical Group, the investigators propensity score matched almost 30 000 VLBW infants 1:1. Early initiation of caffeine therapy was associated with a lower incidence of BPD, 23% compared with 31% in the late group, and a slightly greater incidence of death, 4.5% compared with 3.7%. In addition, early initiation of caffeine therapy was associated with less treatment of a patent ductus arteriosus and a shorter duration of mechanical ventilation. The authors acknowledge the limitations of their observational study design, including the possibility of residual selection bias despite their matching efforts, and conclude that “randomized trials are needed to determine the efficacy and safety of early caffeine prophylaxis in VLBW infants.”

Who should be the target population for a trial of early caffeine prophylaxis to reduce the outcome of BPD or death? We suggest that only fully ventilator-dependent VLBW infants with serious acute lung injury should be eligible. Such infants were unlikely to be enrolled in the CAP trial during the first 3 days of life. Therefore, the benefit-to-risk ratio of caffeine therapy remains uncertain in VLBW infants whose immature respiratory control is concealed by mechanical ventilation. Such infants could be randomly assigned to early caffeine or placebo and switched to open-label caffeine before their first trial of extubation. Of note, a single-center placebo-controlled trial is currently underway at the University of Miami to examine whether caffeine therapy initiated during the first 5 days of life reduces the duration of mechanical ventilation in 110 preterm infants born between 23 and 30 completed weeks of gestation. If this trial confirms that caffeine prophylaxis enables earlier removal of the endotracheal tube in fully ventilated VLBW infants, would we still need additional controlled trials that examine the effect of early caffeine in this population on the outcome of BPD or death? After the first 3 days of life, the level of respiratory support is the single most important predictor of BPD in extremely preterm infants. Therefore, any therapy that reduces the duration of mechanical ventilation will likely reduce the risk of BPD.
How concerned should we be about the excess mortality rate after early caffeine therapy in the observational study by Dobson et al? We agree with the authors that the slightly lower mortality rate in the late caffeine cohort is most likely explained by survival bias because the mean age at initiation of late caffeine therapy was 11 days. The authors excluded only deaths during the first 3 days of life from their analysis. Consequently, all infants in the early caffeine cohort, but only about one-half of the infants in the late caffeine cohort, were at risk of dying between days 4 to 11. There was no evidence in the CAP trial that caffeine had any effect on mortality rates when measured at 3 time points: before discharge, at 18 months, and at 5 years.

Healthy VLBW infants with gestational ages greater than 29 weeks who do not require any respiratory support are at the other end of the illness severity spectrum. These infants should not be enrolled in a trial of early caffeine prophylaxis to reduce BPD or death because their risk of both outcomes is very low. In fact, we do not recommend that such infants be treated with caffeine unless they develop apnea. We make this recommendation despite the possibility that caffeine may have a direct neuroprotective effect in preterm infants. More clinical research is needed before caffeine can be recommended as a neuroprotective agent for VLBW infants who do not require treatment for immature respiratory control and apnea.

All remaining VLBW infants—those who are neither fully ventilated nor stable in room air without manifesting apnea—have a high risk of apnea because of their immaturity and likely receive positive airway pressure without an endotracheal tube or are weaning rapidly towards a trial of extubation during the first few days of life. Such infants should be considered “candidates for methylxanthine therapy.” They would have been eligible for the CAP trial and will benefit from treatment with caffeine at the doses used in this trial and found to be safe up to age 5 years.

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References