Caffeine Duration for Apnea of Prematurity: All Bets Are Off!

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Caffeine is the most commonly used drug for prevention and treatment of apnea of prematurity and, prevention of bronchopulmonary dysplasia (BPD) [1]. However, several issues with respect to caffeine use in preterm infants are still unresolved. These include optimal gestational cutoff for initiating caffeine, the range of effective dose, and the duration of therapy.

Prakash and colleagues explored optimum duration of therapy by comparing continuation of caffeine till 34 wk postmenstrual age (PMA) vs. stopping caffeine after a 7 d apnea-free period, in neonates of 26–32 wk gestation [2]. They were willing to accept a 10% absolute difference in the incidence of ‘recurrence of apnea of prematurity (RAP)’ against a presumed baseline risk of 1% among those given caffeine till 34 wk PMA. They randomized a total of 120 neonates against the calculated sample size of 174 neonates for a superiority trial and reported no significant difference in the incidence of RAP between the two groups. The main reason for not being able to find any difference in RAP, if it did exist, lies in the inadequate power of the study. The observed incidence of RAP in the two groups was far higher (13% and 15%) as compared to the presumed baseline risk of 1% used for sample size estimation, and the observed effect size (2%) was lower than the presumed effect size of 10%.

With the goal of decreasing exposure to caffeine, an ideal study design to answer this research question should be a noninferiority trial, in which the investigators seek noninferiority of a shorter course of caffeine e.g., 7-d apnea-free period compared to caffeine given till 34 wk PMA. The study participants need to be chosen carefully. In the index study, the incidence of RAP in 26–29 wk subgroup was very high—29% vs. 24%, making it a challenge to stop caffeine early in this subgroup. The incidence of apnea after the infants were otherwise ready for discharge, in the

epidemiological data from Kaiser Permanente Medical Care Program hospitals, ranged from 22.8% in 29–30 wk neonates to 26.6% in 27–28 wk neonates [3]. Hence, the potential target group may be neonates > 30 wk gestation in whom the incidence of RAP was 3% and 6% in the two groups. A low noninferiority margin is required for such a study as apnea can be a life-threatening event, especially in resource-constraint settings. As an example, 1794 subjects will be required for a noninferiority trial assuming 96% success rate of stopping caffeine at 34 wk PMA, with a noninferiority margin of 3%, type 1 error of 2.5%, and power of 90%. A trial aimed at reducing the duration of therapy will also have to measure any changes in the incidence of BPD and neurodevelopmental outcomes, which are potentially benefitted by caffeine. Therefore, while the results of the current study do not inform clinical practice, they surely form the basis for future trials to solve this clinical dilemma.

Declarations

Conflict of Interest None.

References

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