Optimizing Caffeine Use and Risk of Bronchopulmonary Dysplasia in Preterm Infants

A Systematic Review, Meta-analysis, and Application of Grading of Recommendations Assessment, Development, and Evaluation Methodology

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KEYWORDS

• Infant • Neonate • Preterm • Caffeine • Methylxanthine • Dose • Timing • Duration

KEY POINTS

- Earlier initiation of caffeine, compared to later initiation, is associated with a decreased risk of bronchopulmonary dysplasia.
- High-dose caffeine, compared to standard-dose caffeine, may reduce the risk of bronchopulmonary dysplasia.
- The overall quality of evidence of studies on the dose and timing of caffeine and risk of bronchopulmonary dysplasia is low.
- Higher-quality evidence is needed to understand the risks and benefits of early initiation and high-dose caffeine to decrease the risk of bronchopulmonary dysplasia.

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INTRODUCTION

Rationale

From the first described use in the 1970s as a treatment of apnea of prematurity,[1,2] caffeine is now one of the most commonly administered medications in neonatal intensive care units worldwide.[3,4] The Caffeine for Apnea of Prematurity (CAP) trial demonstrated several beneficial effects of caffeine in extremely preterm infants, including a lower risk of bronchopulmonary dysplasia (BPD)[5] and death or disability at 18 to 21 months[6] with benefits persisting into middle childhood.[7] A post hoc subgroup analysis of this trial reported a greater reduction in the duration of respiratory support among infants who initiated caffeine early (before day 3) compared with later (3–10 days) in life.[8] Multiple observational studies have also evaluated the timing of caffeine initiation and neonatal outcomes,[9,10] and the optimal timing of caffeine administration for maximal beneficial effect remains the subject of more recent investigation.[11] The standard dosing for caffeine citrate used in the CAP trial was 20 mg/kg loading followed by 5 to 10 mg/kg/d as maintenance.[5] Although some studies have shown respiratory benefits with a higher dose of caffeine,[12] another study raised concerns regarding the potential harms.[13] Additionally, clinicians have used a variety of dosing regimens to balance the optimal benefit of caffeine with the potential for adverse effects in routine practice.[14] Variation also exists in the age at cessation of caffeine therapy.[14,15] The authors' rationale for this review was that given the common use of caffeine in preterm infants, optimizing its use may enhance the known benefits of caffeine therapy.

Objective

The objective of this systematic review was to evaluate the following question: Among preterm infants, does the timing of caffeine initiation, the dose of caffeine, or the duration of caffeine therapy influence clinical outcomes, including BPD?

METHODS

Protocol/Registration

The authors used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to report the systematic review and meta-analysis[16] and registered the protocol with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) on August 31, 2017 (No. 75841).

Eligibility Criteria

Studies: All meta-analyses, randomized controlled trials (RCT), and observational studies were considered for qualitative inclusion. Only individual RCTs and observational studies were quantitatively synthesized. The authors excluded case reports, editorials, and reviews without meta-analyses and resolved discrepancies by consensus of all investigators.

Participants: The participants were infants of less than 37 weeks' gestation.

Interventions: (1) For the timing of initiation, intervention is early initiation of caffeine as defined by the study. (2) For the dose of caffeine, intervention is a high dose as defined by the study or the higher dose for 2 or more comparison groups. (3) For the duration of treatment, intervention is the longer duration of caffeine for 2 or more comparison groups.

Comparators: (1) For the timing of initiation, comparator is the later initiation of caffeine as defined by the study. (2) For the dose of caffeine, comparator is the standard dose or lower dose as defined by the study. (3) For the duration of treatment, comparator is the shorter duration of caffeine for 2 or more comparison groups.