The Role of Caffeine in Noninvasive Respiratory Support

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KEYWORDS

• Caffeine • Apnea • Bronchopulmonary dysplasia • Premature infant
• Noninvasive ventilation

KEY POINTS

- Caffeine is safe, effectively treats apnea, and reduces the risk of bronchopulmonary dysplasia.
- Caffeine facilitates the successful transition from invasive to noninvasive respiratory support and decreases the duration of positive airway pressure support.
- Observational studies suggest early initiation of caffeine within 2 days of birth may have greater benefits compared with later initiation, including fewer days of invasive respiratory support and lower risk of bronchopulmonary dysplasia.
- Additional studies are needed to determine the optimal dose and duration of caffeine therapy and whether prophylactic use of caffeine can prevent the need for rescue interventions among infants receiving early noninvasive respiratory support.

INTRODUCTION

Management of apnea of prematurity plays a critical role in the success of noninvasive ventilation strategies in preterm infants. Methylxanthines have been used in the neonatal intensive care unit for more than 40 years to treat and prevent apnea of prematurity. Among methylxanthines (aminophylline, theophylline, caffeine), caffeine is

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used most commonly because of its wide therapeutic index and longer half-life that allows once-daily administration.[1] Caffeine accounted for 96% of all methylxanthine use in very-low-birth weight (VLBW) infants in 2010.[2] In addition, caffeine is one of the most common medications administered to infants in neonatal intensive care units.[3] Several beneficial effects of caffeine have been well established, whereas other benefits are plausible, and yet others require additional study (**Box 1**). This review focuses on the use of caffeine in preterm infants receiving noninvasive respiratory support with specific emphasis on clinical effects of caffeine, mechanisms of action, timing of initiation, and optimal dose and duration of therapy.

EFFECT OF CAFFEINE ON RESPIRATORY OUTCOMES IN PRETERM INFANTS

Apnea and Intermittent Hypoxia

Despite advances in neonatal care, apnea remains a common and pervasive problem in preterm infants that often leads to failure of noninvasive respiratory support.[4] Apnea can lead to intermittent hypoxia,[5] and intermittent hypoxemic episodes (oxygen saturation <80%) among extremely preterm infants are associated with a higher risk of death or disability at 18 months of age (relative risk 1.53; 95% confidence interval [CI] 1.21–1.94).[6] Caffeine, a trimethylxanthine that primarily exerts its effects by blocking adenosine A1 and A2A receptors, effectively treats apnea[7,8] and reduces intermittent hypoxia.[9] The primary mechanism by which methylxanthines reduce apnea is through antagonism of A2A receptors on GABAergic neurons.[10,11] Caffeine decreases apnea by stimulating the medullary respiratory centers, increasing carbon dioxide sensitivity, and enhancing diaphragmatic function, leading to increased minute

Box 1
Known, potential, and uncertain respiratory benefits of caffeine therapy

Known respiratory benefits of caffeine in infants weighing less than 1250 g at birth

- Decreases apnea episodes in preterm infants[7,8]
- Decreases risk of bronchopulmonary dysplasia[20]
- Decreases duration of positive airway pressure support[20]
- Decreases treatment of a patent ductus arteriosus[20]
- Increases successful extubation within 1 week of initiation of treatment[23]

Potential additional respiratory benefits of early initiation of caffeine in VLBW infants

- May further decrease risk of bronchopulmonary dysplasia[2,42–44]
- May further decrease duration of invasive respiratory support[2,42–44]
- May further decrease duration of noninvasive respiratory support[42]
- May further decrease treatment of a patent ductus arteriosus[2,42–44]

Uncertain respiratory benefits of caffeine in VLBW infants

- Does prophylactic caffeine on the day of birth, compared with later initiation, reduce failure of initial noninvasive respiratory support?
- Does prophylactic caffeine on the day of birth, compared with later initiation, reduce the duration of noninvasive respiratory support?
- Does caffeine improve long-term respiratory health into adolescence?
- Is high-dose caffeine, compared with standard-dose caffeine, a safer and more effective alternative to decrease apnea?