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The Role of Caffeine in Non-Invasive Respiratory Support

Nicole R. Dobson, MD¹ and Ravi Mangal Patel, MD, MSc^{2,*}

¹Department of Pediatrics, Tripler Army Medical Center, 1 Jarrett White Road, Honolulu, HI 96859. Tel 808-433-6534. nicole.r.dobson.mil@mail.mil

²Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, 2015 Uppergate Dr. NE, 3rd floor, Atlanta, GA 30322. Tel 404-727-5905. rmpatel@emory.edu

Abstract

Caffeine is one of the most commonly prescribed medications in preterm neonates and is widely used to treat or prevent apnea of prematurity. Caffeine therapy is safe, effectively decreases apnea and improves short- and long-term outcomes in preterm infants. In this review, we summarize the role of caffeine therapy for preterm infants receiving non-invasive respiratory support. We highlight caffeine's beneficial effects on reducing bronchopulmonary dysplasia and focus on the role of caffeine in facilitating the transition from invasive to non-invasive respiratory support, reducing the duration of respiratory support and the potential for decreasing failure of non-invasive respiratory support. We review the multiple mechanisms of action of caffeine, including its effect on apnea, respiratory mechanics and lung inflammation. As caffeine is already widely used, we summarize recent data that may guide clinicians in optimizing the use of caffeine therapy, with a review of the timing of initiation, dose and duration of therapy.

Keywords

caffeine; apnea; bronchopulmonary dysplasia; premature infant; noninvasive ventilation

Introduction

Management of apnea of prematurity plays a critical role in the success of non-invasive 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 used most commonly because of its wide therapeutic index and longer half-life that allows once-daily

*Corresponding author: Dr. Patel.

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administration¹. Caffeine accounted for 96% of all methylxanthine use in very low birth weight (VLBW) infants in 2010². In addition, caffeine is one of the most common medications administered to infants in neonatal intensive care units³. A number of beneficial effects of caffeine have been well established, while other benefits are plausible and yet others require additional study (Box 1). This review focuses on the use of caffeine in preterm infants receiving non-invasive 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 non-invasive respiratory support⁴. Apnea can lead to intermittent hypoxia⁵ 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% 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 hypoxia⁹. 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 ventilation, improved respiratory pattern, and reduced hypoxic respiratory depression^{1,12}. As discussed later, these and other physiologic effects of caffeine are likely to mediate many of the respiratory benefits of caffeine observed in clinical studies.

Methylxanthines are effective in reducing the frequency of apneic events and the use of mechanical ventilation in the first week after starting treatment⁷. Higher dosing regimens appear to more effectively treat apnea^{13,14}, but a recent pilot study suggests that early high-dose caffeine (80 mg/kg total) given over 36 hours to preterm infants born <30 weeks gestation increases the incidence of cerebellar hemorrhage with subsequent alteration in early motor performance¹⁵. These findings raise concerns about the safety of high-dose caffeine. Although the study found no differences in neurodevelopmental outcomes at 2 years, the findings of increased intracranial hemorrhage parallel non-significant trends of increased grade 3 or 4 intraventricular hemorrhage seen in another trial of high-dose caffeine¹³, and warrant further study to determine the safety of early high-dose caffeine to decrease apnea.

Studies that have evaluated the efficacy of caffeine as prophylaxis to prevent apnea have not shown definitive benefit, with a systematic review concluding that the available evidence does not support the use of caffeine as prophylaxis to prevent apnea¹⁶. However, given the favorable safety profile and common occurrence of apnea among extremely preterm infants, we believe the prophylactic use of caffeine in premature infants to prevent apnea is a reasonable approach among high-risk preterm infants (e.g. birth weight <1250 grams) who may have cardiorespiratory compromise from apnea. A recent cross-sectional survey of neonatologists in Thailand, Lebanon, Australia, and the US revealed that prophylactic use of

methyxanthines for apnea of prematurity is common, with 62% of those surveyed reporting prophylactic use¹⁷. Similarly, caffeine was used for apnea prophylaxis in 37% of preterm infants in a multicenter prospective study in Austria, Czech Republic, Greece, Italy, and Spain¹⁸.

Bronchopulmonary dysplasia

Among VLBW infants receiving respiratory support, bronchopulmonary dysplasia (BPD) is the most common serious chronic lung disease of infancy and can cause long term respiratory problems including decreased lung function and asthma-like symptoms¹⁹. The Caffeine for Apnea of Prematurity (CAP) trial, a large, randomized trial conducted from 1999 to 2004, provides the most comprehensive data regarding the effects of caffeine on short- and long-term neonatal outcomes in infants weighing <1250 grams at birth. While the trial did not specifically evaluate the effectiveness of caffeine in reduction of apnea of prematurity, the study showed that infants treated with caffeine, compared to placebo, had a lower risk of BPD (adjusted odd ratio 0.64; 95% CI 0.52–0.78)²⁰. Other benefits of caffeine demonstrated in the trial included decreased need for treatment of a patent ductus arteriosus, reduced severity of retinopathy of prematurity, and, perhaps most importantly, improved motor function and visual function at 5-year follow-up^{20–22}. The CAP trial did not reveal any significant short- and long-term adverse effects of caffeine therapy, supporting the safety of caffeine use in preterm infants. The association of caffeine with improved clinical outcomes combined with its safety profile has led to a consensus that caffeine is the “preferred drug” for treatment of apnea of prematurity⁷.

Facilitation of transition to non-invasive respiratory support

In preterm infants requiring mechanical ventilation, caffeine therapy facilitates the transition to non-invasive respiratory support. Administration of caffeine around the time of extubation in premature infants results in a significant reduction in the failure of extubation within one week (relative risk 0.48; 95% CI 0.32–0.71)²³. In the CAP trial, caffeine-treated infants had younger postmenstrual ages (PMA) at last use of endotracheal intubation (median 29.1 vs. 30.0 weeks; $P < 0.001$)²⁰. Higher caffeine dosing regimens in the periextubation period may be more effective in preventing apnea and reducing extubation failure rates. A randomized trial of three different maintenance dosing regimens of caffeine citrate (3, 15, and 30 mg/kg) for periextubation management of 127 infants born at less than 32 weeks gestation revealed significantly less apnea in the two higher dose groups compared to the lowest dose group, although there was no difference in extubation failure rates between groups¹⁴. Another trial comparing maintenance dosing regimens of 5 and 20 mg/kg/day of caffeine citrate showed a significant reduction in extubation failure in the high-dose group (relative risk 0.51, 95% CI 0.31–0.85)¹³. A more recent trial in preterm infants born less than 32 weeks gestation comparing high-dose (loading 40 mg/kg/day and maintenance of 20 mg/kg/day) versus low-dose (loading 20 mg/kg/day and maintenance of 10 mg/kg/day) caffeine citrate showed that high-dose caffeine was associated with a significant reduction in extubation failure²⁴. However, the potential benefits of high dose caffeine in reducing extubation failure need to be balanced with safety concerns related to a higher incidence of intracranial hemorrhage among infants receiving highdose caffeine in the first 36 hours of life¹⁵, as previously mentioned.

Duration of respiratory support

Caffeine therapy reduces the duration of non-invasive respiratory support in preterm infants. In the CAP trial, caffeine-treated infants, compared to placebo-treated infants, had younger PMA at last use of positive pressure ventilation (PPV) (median age of 31 weeks vs. 32 weeks; $P < 0.001$) and oxygen therapy (33.6 weeks vs. 35.1 weeks; $P < 0.001$)²⁰. An additional post-hoc subgroup analysis of the CAP trial demonstrated that the effects of caffeine on the PMA at last PPV was consistent across infants who received invasive and non-invasive respiratory support as well as those without PPV at time of randomization (test for heterogeneity $P = 0.80$)²⁵. Current data suggests that high-dose caffeine (20 mg/kg/day maintenance therapy) does not provide additional benefit over standard dosing (5 mg/kg/day maintenance therapy) on the duration of non-invasive respiratory support after extubation^{24,26}.

Reports have suggested that standardizing use of caffeine may reduce the use of invasive respiratory support. A report focusing on non-invasive respiratory support from centers participating in the Vermont Oxford Network-sponsored Neonatal Intensive Care Quality Improvement Collaborative (NIC/Q 2005) showed increases in the routine use of caffeine were temporally associated with fewer days of invasive ventilation but not a lower risk of BPD²⁷. In this study of infants < 30 weeks gestation, caffeine exposure increased from 47% at baseline to 98% post-implementation ($P < 0.001$), with a decrease in median days of ventilation (8.5 vs. 4.0, $P < 0.001$) and a concomitant increase in days of continuous positive airway pressure (CPAP) use (4.0 to 8.0, $P < 0.001$). Although several other practices were changed along with caffeine use limiting any inference of the specific effects of caffeine, these data suggest that standardizing caffeine use is one important component of efforts to improve postnatal respiratory care of preterm infants.

Physiologic effects of caffeine on pulmonary function

Studies in both humans and animals have shown that caffeine has multiple effects on pulmonary function and respiratory health (Figure 1). These effects include improving lung compliance and airway resistance,^{28,29} increasing minute ventilation^{28,30}, increasing diaphragm muscle contractility^{31,32} decreasing lung inflammation^{33–35} and improving airway remodeling³⁶. Although it is unclear which of these potential mechanisms are responsible for the clinical benefits of caffeine observed in large clinical trials, it is likely that multiple mechanisms, beyond a reduction in apnea, are responsible for the benefits of caffeine on pulmonary health. The potential effects of caffeine on improving lung compliance and respiratory muscle function are likely to be important in ensuring infants on non-invasive respiratory support maintain effective ventilation. However, additional investigation is needed to translate the study of effects of caffeine observed in animal studies to preterm infants.

Mechanisms of failure of non-invasive respiratory support

Non-invasive respiratory support is commonly initiated in the delivery room. However, many VLBW infants will need additional “rescue” therapy with surfactant or mechanical ventilation. Data from randomized controlled trials report incidences of CPAP failure

needing “rescue” between 22%–36% for VLBW infants^{37–39} and 46–66% for extremely preterm infants^{40,41}. Those infants who fail CPAP therapy are at higher risk of adverse outcomes, including death or BPD³⁸. As some infants will have an interval of several hours or days between initial non-invasive respiratory support therapy and failure, early caffeine therapy has the potential to decrease failure rates. However, limited studies have evaluated the effect of early caffeine initiation on the risk of initial non-invasive respiratory support failure. Additional prospective studies are needed to determine if prophylactic use of caffeine on the day of birth can improve the success of initial non-invasive respiratory support therapy, especially in extremely preterm infants.

Timing of caffeine initiation in infants receiving non-invasive respiratory support

Several studies have demonstrated an association with earlier initiation of caffeine in the first few days of life, compared to later initiation, and improved respiratory outcomes in preterm infants, including a reduced risk of BPD^{2,42–44} and shorter duration of respiratory support with ventilation or CPAP therapy^{2,25,43}. In a post-hoc subgroup analysis of the CAP trial, the effect of caffeine, compared to placebo, on the PMA at last PPV appeared greater for infants initiating caffeine within the first 3 days of age compared to later initiation (mean difference: early, –1.35 days vs. late –0.55 days, test for heterogeneity adjusted $P=0.03$)²⁵.

In an initial study reporting the comparative effectiveness of early (initiation < 3 days of life) vs. late (initiation at or after 3 days of life) caffeine therapy at a single center, early caffeine therapy was associated with a lower risk of BPD (adjusted odds ratio 0.26, 95% CI 0.09–0.70; $P<0.01$) and shorter duration of invasive ventilation (median 6 vs 22 days, $P<0.01$)⁴³. Subsequently, three large multicenter cohort studies in the US and Canada have confirmed these findings^{2,42,44}. In a multicenter cohort study of 62,056 VLBW infants who were propensity-matched to reduce confounding, early caffeine initiation was associated with a lower risk of BPD (odds ratio 0.68; 95% CI 0.69–0.80) and a shorter duration of mechanical ventilation (median 3 vs. 6 days, $P<0.001$) compared to infants receiving late caffeine². In a large multicenter cohort study in Canada of infants born before 31 weeks gestation, infants receiving early caffeine in the first 2 days of life, compared to later caffeine, had a shorter duration of invasive mechanical ventilation and a shorter duration of non-invasive respiratory support⁴². Early caffeine use in this study was also associated with a decreased risk of BPD (adjusted OR 0.79; 95% CI 0.64–0.96) and surgical treatment of a patent ductus arteriosus (adjusted OR 0.58; 95% CI 0.42–0.80). Similar findings of a decrease in the risk of BPD associated with early caffeine (0–2 days of age), compared to later initiation (3–10 days) were reported in a study of 2,951 infants weighing ≥ 1250 grams at birth (adjusted odds ratio 0.69; 95% CI 0.58–0.82)⁴⁴. However, this study reported an increased risk of necrotizing enterocolitis (NEC) among infants receiving early caffeine (adjusted odds ratio 1.41; 95% CI 1.04–1.91)⁴⁴. By contrast, none of the other studies evaluating the effects of early initiation of caffeine, compared to later initiation, found an association between early caffeine exposure and NEC^{2,42,43}.

A recent pilot randomized trial evaluated the use of early prophylactic caffeine very soon after birth⁴⁵. In this study, infants <29 weeks gestation were randomized to early prophylactic use of caffeine before 2 hours of age or caffeine initiation at 12 hours of age. The study reported fewer infants in the early caffeine treatment arm required intubation by 12 hours of age, compared to those receiving caffeine at 12 hours of age, although this was not a statistically significant difference (27% vs 70%, $P=0.08$). By contrast, there was no reduction in days of mechanical ventilation between infants receiving caffeine before 2 hours vs. 12 hours of age (mean 6 days vs. 3 days; $P=0.40$). Additional studies are necessary to determine if prophylactic caffeine can successfully prevent the need for intubation among preterm infants initially supported with non-invasive respiratory modalities.

Dose and duration of caffeine therapy

Pharmacodynamic studies investigating the relationship between caffeine dose, plasma concentrations, and ventilatory responses show a rapid rise in minute ventilation followed by a plateau in response with increasing doses of caffeine⁴⁶. These observations resulted in the widely used regimens of a loading dose followed by daily maintenance therapy. Approval of caffeine citrate by the Food and Drug Administration for the treatment of apnea of prematurity was based on the standard dosing regimen of a loading dose of 20 mg/kg (10 mg/kg of caffeine base) followed by a daily maintenance dose of 5 mg/kg⁸. This dosing regimen usually achieves plasma caffeine concentrations of 8 to 20 mg/L in infants less than 32 weeks PMA. After 32 weeks PMA, and particularly after 36 weeks PMA, caffeine metabolism increases and the standard dosing regimen may result in sub-therapeutic levels⁴⁷. Higher doses may be required beyond 36 weeks PMA to maintain therapeutic effects.

As discussed previously, some studies have reported that higher doses of caffeine may be more efficacious in facilitating extubation and reducing the frequency of apnea^{13,14,24,26,48}. In the United States, most neonatal centers currently use a maintenance dose of 5 to 10 mg/kg/day of caffeine citrate for routine therapy. However, some international centers have reported use of maintenance doses of up to 20 mg/kg/day^{13,24}. Maintenance doses up to 30 mg/kg/day have been reported without significant adverse effects, and preterm infants have been shown to safely tolerate caffeine concentrations as high as 50–84 mg/L^{13,14,26}. However, safety concerns still exist with the use of early high-dose caffeine, particularly with the recent report of increased rates of cerebellar hemorrhage in infants exposed to early high-dose caffeine¹⁵, and further study is warranted.

Studies suggest that measurement of serum caffeine concentration is not routinely needed, as most preterm infants, including those with hepatic and renal impairment, attain goal plasma levels with current dosing regimens^{49,50}. A recent retrospective study associated higher average caffeine concentrations in infants less than 30 weeks gestation with improved outcomes, including a decreased duration of ventilation, lower incidence of BPD, and shorter duration of supplemental oxygen use⁵¹. Confirmation of these findings in a prospective study may guide additional studies to identify the optimal dosing and therapeutic levels of caffeine.

Caffeine treatment is usually terminated at 33 to 35 weeks PMA following resolution of clinically apparent apnea¹. In the CAP trial, the median PMA at discontinuation of caffeine was 34 weeks²⁰. Extended caffeine therapy in preterm infants nearing initial hospital discharge has been shown to reduce intermittent hypoxia, especially in infants at 35 and 36 weeks PMA⁹. However, the routine practice of extended caffeine therapy cannot be recommended at this time since it is unknown whether intermittent hypoxia adversely affects outcomes in preterm infants nearing term-equivalent age.

Conclusions

Caffeine has an important role in non-invasive respiratory support by facilitating transition from invasive to non-invasive support, reducing the duration of positive airway pressure support, and decreasing the risk of BPD. Multiple mechanisms of action beyond a reduction in apnea are likely to mediate the beneficial effects of caffeine. Additional studies are necessary to guide optimal use of caffeine, including treatment decisions on the dose, duration and timing of therapy.

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Abbreviations

VLBW	very low birth weight
BPD	bronchopulmonary dysplasia
CAP	Caffeine for Apnea of Prematurity
PMA	postmenstrual age
PPV	positive pressure ventilation
CPAP	continuous positive airway pressure
NEC	necrotizing enterocolitis

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(* denotes systematic reviews and meta-analyses)

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Key Points

- Caffeine is safe, effectively treats apnea, and reduces the risk of bronchopulmonary dysplasia.
- Caffeine facilitates the successful transition from invasive to non-invasive 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 to 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 non-invasive respiratory support.

Box 1**Known, Potential and Uncertain Respiratory Benefits of Caffeine Therapy****Known respiratory benefits of caffeine in infants weighing <1250 grams at birth**

- Decreases apnea episodes in preterm infants^{7,8}
- Decreases risk of bronchopulmonary dysplasia²⁰
- Decreases duration of positive airway pressure support²⁰
- Decreases treatment of a patent ductus arteriosus²⁰
- Increases successful extubation within 1 week of initiation of treatment²³

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 non-invasive respiratory support⁴²
- 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 to later initiation, reduce failure of initial non-invasive respiratory support?
- Does prophylactic caffeine on the day of birth, compared to later initiation, reduce the duration of non-invasive respiratory support?
- Does caffeine improve long-term respiratory health into adolescence?
- Is high-dose caffeine, compared to standard dose caffeine, a safer and more effective alternative to decrease apnea?

Figure 1. Effects of Caffeine on Neonatal Respiratory Health: Potential Mechanisms
Study references are noted in the bottom right of each box.