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Caffeine for the management of apnea in preterm infants

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Summary

Considerable uncertainty persists regarding the efficacy and safety of methylxanthines (caffeine, theophylline – in intravenous form named aminophylline) for the prevention and treatment of infant apnea. To help inform national guideline development in Kenya we undertook structured literature searches to identify current evidence on caffeine therapy for infant apnea. Available evidence shows that caffeine is as effective as intravenous theophylline (aminophylline), but is safer and easier to give and has better therapeutic properties. It is therefore recommended for the treatment of apnea of prematurity. Caffeine is also the preferred drug if clinicians plan to provide apnea prophylaxis. As prematurity is likely to result in more than 1 million deaths a year, mostly in resource-poor settings, greater efforts need to be made to ensure interventions such as caffeine, currently unavailable in countries such as Kenya, are made more widely available.

Keywords

Infant; Apnea; Prematurity; Caffeine

1. Introduction

Current management strategies for infant apnea – defined as cessation of breathing for more than 15 seconds accompanied by bradycardia or hypoxia – include the use of methylxanthines (caffeine, theophylline – in intravenous (IV) form named aminophylline) and application of assisted ventilation therapy.[1] These two widely used methylxanthines – caffeine and theophylline – are typically prescribed in preterm infants till a gestational age of 34 to 35 weeks. Despite their widespread use, considerable uncertainty persists regarding their efficacy and safety in the prevention and treatment of apnea in preterm infants. Practically, caffeine citrate is available in injection and oral 20 mg/mL preparations in high income settings. The recommended loading dose of caffeine citrate is 20 mg/kg orally or intravenously followed by 5 mg/kg daily oral (or IV over 30 minutes) maintenance doses.[2] The recommended loading dose of theophylline is 5–6 mg/kg, followed by maintenance doses of 2–6 mg/kg/day divided into two or three doses.[3] Because there is no IV preparation of theophylline, the drug aminophylline, which is approximately 80% theophylline, is commonly used.[4] As neither caffeine nor theophylline in a suitable oral preparation is

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available in Kenya for the management of infant apnea, aminophylline is the most widely used drug. It is given as a loading dose of 5–7 mg/kg IV,and maintenance dose 1.5–2.0 mg/dose every 6–8 hours IV if safe, slow infusion is possible (rare) or rectally where IV administration is deemed unsafe. In this review, we summarise emerging evidence supporting the use of caffeine citrate for treatment of apnea in preterm babies. We particularly highlight pharmaceutical and practical issues associated with caffeine therapy to contribute to debate on the most appropriate treatment for preterm infants in resource-poor settings such as Kenya.

2. Methodology

The Cochrane Library and PubMed (both up to February 2009) were searched for systematic reviews (SRs) and randomized controlled trials (RCTs) of caffeine therapy in apnea of any cause. PubMed was searched via the Clinical Queries search filter: 'therapy, narrow specific' search without any language or temporal limits by date of publication. The combination of keywords used was: apnea AND (prematur* OR preterm OR very low birth weight OR low birth weight) AND (caffeine OR methylxanthine* OR aminophylline OR theophylline). Bibliographic references of retrieved reviews and studies were searched for additional articles. Only studies enrolling preterm infants treated with caffeine or other methylxanthines were considered. The primary outcomes evaluated were death or long-term neurodevelopmental outcome. We also considered, where reported, the following short term outcomes: frequency of apnea, use of assisted ventilation, growth, adverse effects and neonatal morbidity. Two reviewers independently screened the titles and abstracts based on the predetermined study selection criteria, with disagreements being referred to a third reviewer.

3. Results

We identified 151 references through the electronic and supplementary searches. After reading the titles and abstracts of the articles we excluded 141 irrelevant references and retrieved 10 potentially relevant references for further detailed assessment. We further excluded 4 RCTs[5,10,12,13] which were included in three Cochrane reviews.[6,7,11] Overall, we have considered 6 studies (4 Cochrane reviews (n = 348 patients)[6,7,9,11] and 2 RCTs (n = 2006 patients)[1,8] published after the Cochrane reviews.

The treatments evaluated in the included studies were caffeine vs. theophylline[6] and caffeine or theophylline vs. placebo or no treatment.[1,7,8,11] The loading doses of caffeine ranged from 5 to 20 mg/kg while maintenance doses ranged from 1.25 to 5 mg/kg/day in the included studies. Outcomes assessed included: survival without neurodevelopmental disability,[8] frequency of apneic episodes[6,9] use of assisted ventilation[7,9,11] bronchopulmonary dysplasia (defined as the need for supplemental oxygen at 36 weeks postconceptional age)[1] and a variety of adverse events (death, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), etc). The characteristics of the included studies are summarised in Table 1. We did not retrieve any reviews or RCTs reporting the efficacy of aminophylline given rectally.

3.1. Caffeine compared with placebo for treatment of apnea caused by prematurity

A SR[11] which considered three methylxanthines (theophylline, aminophylline and caffeine) found two RCTs[5,10](n = 100) which examined the effects of caffeine (compared to placebo) on treatment failure (less than 50% reduction in apnea), or use of intermittent positive pressure ventilation (IPPV), or death during study. The two trials found significantly lower treatment failure with caffeine therapy (RR 0.46, 95% confidence interval (CI) 0.27, 0.78; risk difference (RD) −0.31, 95% CI −0.49, −1.2, number needed to treat (NNT) 3, 95% CI 2,

3). Data on adverse effects was reported by one trial[5] which reported that no infants had side effects such as tachycardia or feed intolerance.

The largest RCT to date[1] (n = 2006) – a multicentre placebo controlled RCT – evaluated both short-term (bronchopulmonary dysplasia, brain injury, retinopathy of prematurity (ROP), necrotising enterocolitis (NEC) and growth) and long-term (survival without neurodevelopmental disability) effects of caffeine therapy in very low birth weight infants. The indications for infant inclusion were need of methylxanthine for treatment in 40% (n = 802), prophylaxis prevention of apnea in 22% (n = 441), or prophylaxis for extubation in 38% (n = 762) of infants. The overall results of this study, without subgroup analyses based on the indication for enrolment, were reported in two parts: In the first paper,[1] IV caffeine substantially reduced the need of supplemental oxygen (odds ratio (OR) 0.63, 95% CI 0.52, 0.76, P < 0.001). Caffeine therapy was initially associated with a reduction in the rate of weight gain: however, there was no significant difference in the rate of weight gain after 3 weeks. Additionally, no statistically significant difference was found between groups with regard to short-term mortality, brain injury, ROP or NEC.

In the second paper[8] based on the same patient group, caffeine significantly improved the rate of survival without neurodevelopmental disability at 18–21 months (OR 0.77, 95% CI 0.64, 0.93, P = 0.008). The number of infants who would need to be treated with caffeine to prevent one adverse outcome was 16, 95% CI 9, 56. Caffeine therapy was associated with a significant reduction in the rate of cerebral palsy (OR 0.59, 95% CI 0.39, 0.89) and the incidence of cognitive delay (OR 0.83, 95% CI 0.67, 1.02) at 18 to 21 months. There was no statistically significant difference in the rates of death, deafness, blindness, and mean percentiles for height, weight and head circumference between groups.

3.2. Caffeine compared with theophylline for treatment of apnea caused by prematurity

One SR[6] (3 RCTs,[12-14] n = 66) which assessed the effects of both oral[12] and IV[13-14] caffeine (on preterm infants being treated for apnea of prematurity) compared to IV theophylline (aminophylline) found no difference in failure rate (<50% reduction in apnea/bradycardia) between the two drugs. The standard dose of caffeine therapy was associated with a higher rate of apnea after one to three days treatment compared to theophylline and higher dose caffeine (weighted mean difference, WMD 0.40 episodes per 100 minutes, 95% CI 0.33, 0.46). However, no difference in apnea rate between caffeine and theophylline was found after five to seven days treatment. Also, adverse effects (tachycardia/feed intolerance) were lower in the caffeine group. The authors concluded that caffeine appears to be as effective as IV theophylline (aminophylline) in the short term for reducing apnea and is better tolerated and easier to give.

3.3. Caffeine prophylaxis for prevention of apnea

3.3.1. Apnea caused by prematurity—One SR[7] which investigated the effect of prophylactic treatment with methylxanthine found two RCTs (n = 104)[15,16] which assessed the effects of prophylactic IV caffeine. There were no differences between the caffeine and placebo groups in either of the studies in the number of infants with apnea, bradycardia, hypoxemic episodes, use of IPPV, or side effects. The authors concluded that current available data do not support the use of prophylactic caffeine to prevent apnea in preterm infants at risk of apnea.

3.3.2. Post anesthesia apnea—Another SR[9] (3 RCTs,[17-19] n = 78) which examined the effect of prophylactic IV caffeine compared to placebo on post-operative apnea following anesthesia reported fewer incidences of apnea/bradycardia in infants treated with caffeine (Risk ratio, RR 0.09, 95% CI 0.02, 0.34). Fewer than two infants needed to be treated with

caffeine to prevent one infant with post-operative apnea (Absolute RD −0.58, 95% CI −0.74, −0.43). Caffeine was associated with significantly fewer hypoxemic episodes (<90%) (RR 0.13, 95% CI 0.03, 0.63). No adverse effects were reported. The authors concluded that caffeine given at the time of surgery may be able to prevent post-operative apnea and bradycardia in preterm babies.

4. Discussion

4.1. Interpretation of results

Our aim is to use the best available evidence to inform development of national guidelines in a resource poor setting, Kenya. We did not set out to perform or update systematic reviews. We interpret the evidence as showing that caffeine treatment (compared to placebo) is effective in reducing apnea caused by prematurity. Caffeine therapy was also associated with both long-term (improved rate of survival without neurodevelopment sequelae) and short-term benefits (reduced use of IPPV and reduced rate of broncho-pulmonary dysplasia). Adverse effects were relatively low with caffeine treatment. Thus, with a probable NNT of 3-16,[8],[11] the above benefits would be achieved with few preterm infants being exposed to the adverse effects of caffeine. The findings from the multicentre RCT also suggest a possible correlation between apnea and neurodevelopmental outcome – a reduction in the frequency of episodes of apnea may be accompanied with improvement in long-term survival. Caffeine was found to have similar short-term effects on apnea as IV theophylline (aminophylline), less (short-term) adverse effects and better therapeutic properties (i.e. larger gap between therapeutic and toxic blood levels and a longer half-life that allows once daily administration) compared to IV theophylline (aminophylline) and has reliable enteral absorption. Thus, although studies are exclusively from countries with few resource limitations it seems reasonable to conclude that even in resource poor settings caffeine would be preferred to theophylline or aminophylline for the treatment of apnea of prematurity.

Evidence on the effect of caffeine for prevention of apnea (caffeine prophylaxis) is however mixed: no beneficial effect was demonstrated for apnea due to prematurity in one SR[7] (n = 104). However, post-hoc subgroup analysis of the Schmidt et al data (n = 441) (reported only in an abstract[20]), points to some beneficial effect by clinical indication (treatment, prevention, or extubation). These post-hoc findings on prophylactic caffeine use from a well conducted RCT (given the large sample of infants studied compared with those included in the SR[7] (441 vs. 104)) indicate its probable value in this clinical context. Taken together the findings of this large RCT and those of earlier SRs provide strong evidence that caffeine given at the time of operation should reduce episodes of post-operative apnea and strong evidence that caffeine is beneficial in the short and long term for treatment of apnea of prematurity.

4.2. Availability, cost and pharmaceutical considerations

The average wholesale price for caffeine citrate is approximately US$15 per 3 ml vial in the United States,[21] and the equivalent of US$8 for 1 ml ampoules containing 10 mg/ml caffeine citrate in the United Kingdom (UK).[22] However, we were unable to find data on the pricing of caffeine in Kenya and no available evidence of its use in Kenya. Informal enquiries also indicated that this drug is unavailable in Tanzania, Uganda and Malawi despite being on the WHO essential drug list for children. The IV formulation of aminophylline (the most commonly used alternative in Kenya) is available in 25 mg/5 ml ampoules. The local price for 25 mg/ml IV ampoule is US$0.07,[23] compared with a UK price of approximately US$1,[22] with theophylline 50 mg/5 ml syrup being the oral alternative.

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Thus, despite overwhelming evidence of safety and effectiveness and consequent widespread use in higher income countries, use of caffeine therapy remains appalling low in sub-Saharan Africa where at least 1.16 million newborns die every year in the first month of life (with prematurity being a direct cause in 25% of these deaths).[24] Instead apnea of prematurity is either not treated or often treated with rectal administration of IV aminophylline for which evidence of efficacy is lacking. Possible reasons for the limited availability of caffeine, an apparently simple and cost-effective therapy include (i) failure to consider neonatal interventions as important components of child survival programmes, (ii) weak evidence to policy links in most resource-poor health systems, iii) inadequate demand generation amongst influential practitioners and, iv) inadequate attention to supply-side planning and forecasting.

4.3. Summary

Reviewed data provides strong evidence for the effectiveness and safety of caffeine in the treatment of apnea of prematurity. Caffeine is therefore recommended for the treatment of infant apnea and is preferred to theophylline and aminophylline. Although based on limited data, caffeine also appears to be effective in preventing postoperative apnea in preterm infants. Unfortunately, this simple, safe and effective therapy is not available in Kenya. In this regard it is an example of a neglected drug for a neglected condition in a neglected population. As prematurity is likely to result in more than 1 million deaths a year, mostly in resource-poor settings, greater efforts need to be made to ensure interventions such as caffeine are made more widely available.[25]

Clinical Bottom Line
Caffeine is effective and safe for the treatment of apnea of prematurity and for the prevention of apnea after extubation.
Caffeine is as effective as IV theophylline (aminophylline), but is safer and easier to give and has better therapeutic properties. It is therefore preferred for the treatment of apnea of prematurity.
There is some (limited) evidence of effectiveness of caffeine prophylaxis for prevention of infant apnea. Caffeine prophylaxis is therefore recommended if deemed clinically necessary (for example in preterm infants at high risk of developing apnea).

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Table 1

Characteristics of included studies

a) Systematic reviews

Citation	Sample Size	Participants	Interventions	Results
Steer 2001	3 RCTs *n* = 66	Preterm infants (mean gestational age 30 weeks)	*Standard caffeine:* loading dose (10–12.5 mg/kg), maintenance dose (1.25–3.0 mg/kg/12 hours) *Theophylline:* loading dose (5.5–7.5 mg/kg), maintenance dose (2 mg/kg/12 hours, aiming for plasma levels of 5–20 mg/kg)	No significant difference in failure rates (<50% reduction in apnea/bradycardia) between groups Significantly higher rate of apnea in standard dose of caffeine group at 1–3 days (WMD 0.40, 95% CI 0.33, 0.46/100 minutes) No difference in apnea rate at 5–7 days Significantly lower adverse effects (tachycardia/feed intolerance) in caffeine group (RR 0.17, 95% CI 0.04, 0.72)
Henderson 2001	2 RCTs *n* = 100	Preterm infants (26–35 weeks gestational age)	*Caffeine citrate:* loading dose (10–20 mg/kg base), maintenance dose 2.5–5 mg/kg *Placebo:* citric acid/sodium citrate	Caffeine therapy associated with significantly less treatment failure: RR 0.46, 95% CI 0.27, 0.78; RD −0.31, 95% CI −0.49, −0.12; NNT 3, 95% CI 2, 8. No significant difference in the rate of death before discharge, and use of mechanical ventilation. Side effects were not estimable
Henderson 2001b	3 RCTs *n* = 78	Preterm infants (30–32 weeks), term equivalent age (40–44 weeks)	Caffeine (5–10 mg/kg) vs. placebo	Few incidences of apnea/bradycardia in infants treated with caffeine compared to placebo: RR 0.09, 95% CI 0.02, 0.34; RD −0.58, 95% CI −0.74, −0.43 Fewer than two infants needed to be treated with caffeine to prevent one from post operative apnea. Hypoxemic episodes detected in fewer treatment (caffeine) than control infants: RR 0.13, 95% CI 0.03, 0.63. No infants required intubation or mechanical ventilation. No side effects were reported.
Henderson 1999	2 RCTs	Preterm infants	*Caffeine citrate:* loading	No difference between

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a) Systematic reviews

Citation	Sample Size	Participants	Interventions	Results
	n = 104	less than 34 (31–33) weeks gestation age	dose (10–20 mg/kg), maintenance dose (5 mg/kg) *Placebo:* saline	caffeine and placebo in episodes of apnea, bradycardia, hypoxemic episodes, use of IPPV or side effects.

b) Randomised controlled trials

Citation / Design	setting	Sample Size / Participants	Interventions	Results
Schmidt 2007 Multicentre, randomised, placebo-controlled trial	United States, Canada, Australia, Europe, Israel	*n* = 2006 VLBW infants (500-1250 g)	*Caffeine citrate:* 20 mg/kg loading dose given IV followed by 5 mg/kg/day IV or enterally (*n* = 937) *Placebo:* equivalent volume of normal saline (*n* = 932)	Caffeine improved the rate of survival without neurodevelopmental disability at 18–21 months: OR 0.77, 95% CI 0.64, 0.93, P = 0.008 Caffeine associated with a significant reduction in the incidence of cerebral palsy (adjusted OR 0.58, 95% CI 0.39, 0.87, *P* = 0.009) and cognitive delay (adjusted OR 0.81, 95% CI 0.66, 0.99, *P* = 0.04) The number of infants who would need to be treated with caffeine to prevent one adverse outcome was 16 (95% CI 9, 56) No significant difference between groups in rates of death, deafness, blindness, and mean percentiles for height, weight and head circumference
Schmidt 2006 Multicentre, randomised, placebo-controlled trial	United States, Canada, Australia, Europe, Israel	*n* = 2006 VLBW infants (500–1250 g)	*Caffeine citrate:* 20 mg/kg loading dose given IV followed by 5 mg/kg/day IV or enterally (*n* = 963) Placebo: equivalent volume of normal saline (*n* = 954)	Caffeine significantly reduced rates of bronchopulmonary dysplasia: OR† 0.64, 95% CI 0.52, 0.78 Caffeine therapy was associated with significantly less use of positive airway pressure (*P* < 0.001) Caffeine reduced weight gain temporarily, with greatest difference occurring at 2 weeks (MD −23g, 95% CI −32, −13, *P* < 0.001) No significant difference between groups in rates of death, brain injury, ROP and NEC

WMD – weighted mean difference; RR – relative risk; RD – risk difference; NNT – number needed to treat; IPPV – intermittent positive pressure ventilation.

VLBW – very low birth weight; NEC – necrotizing enterocolitis; ROP – retinopathy of prematurity; MD – mean difference; OR – odds ratio

† adjusted for center and patient characteristics.

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