Continuous positive airway pressure versus methylxanthine for apnoea in preterm infants

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Abstract

Rationale: Recurrent apnoea is common in preterm infants, particularly at very early gestational ages. These episodes of ineffective breathing can lead to hypoxaemia and bradycardia, sometimes severe enough to require resuscitation, including positive pressure ventilation. Various interventions have been used to manage apnoea of prematurity, including methylxanthines and continuous positive airway pressure (CPAP). However, CPAP and methylxanthines remain the most widely studied and utilised treatments due to their greater benefits and lesser harms compared to alternatives like CO_2 inhalation. Objectives: To evaluate the benefits and harms of CPAP compared to methylxanthines for apnoea of prematurity in preterm infants. Search methods: We searched CENTRAL, MEDLINE, Embase, CINAHL, three clinical trials databases, and conference proceedings. We checked references in included studies and related systematic reviews up to August 2024. Eligibility criteria: We included all trials using random or quasi-random allocation to CPAP or any methylxanthine in preterm infants with clinical recurrent apnoea with or without bradycardia. We excluded infants with secondary apnoea, defined as apnoea secondary to causes other than prematurity. We excluded cross-over studies since the severity of apnoea of prematurity can change in either direction over time, but most commonly improves with time. We excluded studies that evaluated combined interventions, such as CPAP plus methylxanthines versus either CPAP or methylxanthines alone. Outcomes: Our critical outcomes were failure of treatment at any time point during hospitalisation, neurodevelopmental outcomes assessed at 18 to 24 months, death in the first year from any cause, bronchopulmonary dysplasia at 36 weeks' postmenstrual age (PMA), and adverse effects such as nasal trauma, tachycardia within the first 24 hours of treatment initiation, feeding intolerance, and pneumothorax. Risk of bias: We used the Cochrane risk of bias tool (RoB 1) to assess the risk of bias in the studies. Synthesis methods: We conducted a structured narrative synthesis based on the Synthesis Without Meta-analysis (SWiM) reporting guidelines, as only one eligible study was included. We grouped results by outcome, and extracted absolute and relative effects. No meta-analysis or subgroup analysis was performed. Included studies: We included one small randomised controlled trial (RCT) with a total of 32 participants, conducted in a high-resource setting and involving preterm infants. The trial compared CPAP and theophylline. Synthesis of results: CPAP compared to theophylline. The evidence is very uncertain about whether there is any difference between CPAP and theophylline in failure of treatment during hospitalisation (risk ratio (RR) 2.89, 95% confidence interval (CI) 1.12 to 7.47; risk difference (RD) 0.42, 95% CI 0.11 to 0.74; 1 study, 32 participants; very low-certainty evidence). The evidence is very uncertain about whether there is any difference between CPAP and theophylline in death in the first year (RR 2.57, 95% CI 0.97 to 6.82; 1 study, 32 participants; very low-certainty evidence). In terms of adverse effects, nasal trauma, feeding intolerance, and pneumothorax were not reported. Only tachycardia was reported, but the evidence is very uncertain about whether there is any difference between CPAP and theophylline in tachycardia within the first 24 hours after treatment initiation (RR 0.10, 95% CI 0.01 to 1.60; 1 study, 32 participants; very low-certainty evidence). Bronchopulmonary dysplasia at 36 weeks' PMA and neurodevelopmental outcomes at 18 to 24 months were not reported in the included study. The overall risk of bias is high due to baseline imbalances, lack of blinding, and early trial cessation, which affects the reliability of the findings. Authors' conclusions: From the single, small included study, performed more than 40 years ago, we are very uncertain whether there is any clinically meaningful difference in the effect of CPAP and theophylline on apnoea of prematurity. Both interventions, CPAP and theophylline, have largely been replaced by nasal prong CPAP and caffeine or aminophylline in modern neonatal care, limiting the applicability of these findings to current practice. However, since caffeine is not readily available in some low- and middle-income countries, and CPAP access remains limited in certain settings, further research may still be relevant. If further trials are conducted, these should use modern CPAP delivery methods and caffeine rather than theophylline. This is the second update of a review first published in 1998. Registration: This is an update of the existing review 'Continuous positive airway pressure versus theophylline for apnoea in preterm infants' originally published in The Cochrane Library, Disk 2, 1998 (Henderson-Smart d) and updated on Disk 4, 2001 (Henderson-Smart e). Previous versions are available via DOI: 10.1002/14651858.CD001072. The title was amended from 'Continuous positive airway pressure versus theophylline for apnoea in preterm infants' to 'Continuous positive airway pressure versus methylxanthine for apnoea in preterm infants' in May 2024.

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