

Is caffeine useful in the prevention of apnoea of prematurity?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *Is caffeine useful in the prevention of apnoea of prematurity?*

The WHO Pocketbook of Hospital Care for Children recommends caffeine citrate and aminophylline to prevent apnoea in premature babies, caffeine is preferred if it is available. The loading dose of caffeine citrate is 20 mg/kg orally or i.v, a maintenance dose should be prescribed. If an apnoea monitor is available this should be used. (Pocketbook chapter 3.10.3, page 55).

INTRODUCTION

Although all premature neonates, as well as many full-term neonates, have periodic respiration pauses, these are usually brief and cause no physiological changes. Apnoea is cessation of respiration exceeding an arbitrary duration of 20 seconds, or less than 20 seconds but with bradycardia or oxygen desaturation [1].

Prolonged apnoea may lead to hypoxaemia and reflex bradycardia, and may increase the risk of intraventricular haemorrhage, hydrocephalus and abnormal neurological development during the first year of life [2]. Frequent episodes of apnoea require ventilatory support using continuous positive airway pressure (CPAP), or intubation and mechanical ventilation [3].

The use of methylxanthines, of which caffeine is a member, has been evaluated in a Cochrane Review. Caffeine has been shown to reduce the number of apnoeic episodes and the requirement for mechanical ventilation when given to premature neonates who are having apnoea [3]. This current review attempts to establish whether prophylactic use of caffeine in a population of otherwise well premature neonates can prevent apnoea of prematurity, and its associated bradycardia and hypoxia.

METHODOLOGY

The MeSH terms 'caffeine', 'apnea', 'infant;premature' and 'premature birth' were utilised.

Initially, the Cochrane Library was searched with the simple search strategy 'caffeine AND apnea AND prematurity'. Nine Cochrane Reviews were retrieved, of which one looked specifically at prophylactic methylxanthine for prevention of apnoea in preterm infants [4]. A further review assessed prophylactic caffeine in the prevention of postoperative apnoea in preterm infants following general anaesthesia [5]. The Cochrane Central Register for Controlled Trials (CENTRAL) was searched concurrently.

The PubMed 'Clinical Queries' framework was utilised to search for more recent studies on use of caffeine in apnoea of prematurity. Papers regarding prophylactic or preventative use of caffeine were favoured. The search strategy employed was as follows: (caffeine AND apnea AND prematurity) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])).

Clinical filters for both 'therapy' and 'narrow, specific' were used, and no new relevant papers were identified. Reference lists were handsearched and abstracts were read. Where relevance was in doubt, the complete article was sourced.

Articles were restricted to the English language. When searching on PubMed, papers older than the most recent update to the Cochrane Review were excluded to prevent duplication of findings. Methodological quality of selected articles was assessed using the Oxford Centre for Evidence-Based Medicine Levels of Evidence.

The recommendations have been summarised below.

RESULTS

The evidence for the use of prophylactic methylxanthine (caffeine) for the prevention of apnoea in preterm infants was the topic of a Cochrane Review last updated in November 2004 [4]. This systematic review was evidence level 1a, and identified two high quality randomised controlled trials examining a total of 104 infants [6,7]. In both studies, the caffeine and placebo groups were comparable, and meta-analysis of the two outcomes common to the studies - i.e. use of intermittent positive pressure ventilation and tachycardia - found no significant differences between treatment and placebo groups.

In one of the trials however, 30 patients of 54 (56%) were followed up [7]. This was incomplete and reported by apnoea incidence rather than trial treatment group.

A second Cochrane Review identified three randomised controlled trials assessing prophylactic use of intravenous caffeine during general anaesthesia in ex-preterm infants [5]. By term-equivalent age, the tendency towards spontaneous apnoea tends to have gone, however depression of the central nervous system such as during general anaesthetic may cause further apnoeas and oxygen desaturations. In each trial, fewer apnoeic / bradycardic episodes occurred in the treated than in the control infants. Typical evidence for relative risk is 0.09 (0.02, 0.34), and absolute risk difference is -0.58 (-0.74, -0.43) indicating that fewer than two infants required treatment with caffeine to prevent one with postoperative apnoea. No infant required intubation or mechanical ventilation, and there were no adverse effects. Completeness of follow up was not clearly stated.

DISCUSSION

The number of infants identified by the first Cochrane Review (104) is small and thus statistical analysis was only able to detect large differences. Of the two trials assessed, one measured mild bradycardia and hypoxaemia as outcomes rather than apnoea itself [6]. The second trial recorded events of apnoea and bradycardia and found no significant differences between infants receiving prophylactic caffeine and placebo [7].

Some evidence was found that prophylactic caffeine may be given to ex-preterm infants to prevent postoperative apnoea / bradycardia following general anaesthesia [5]. Only 78 participants were included, so it is not possible to exclude less common adverse effects. Though fewer apnoeic / bradycardic episodes occurred in treated than control infants, it is unclear whether these episodes are clinically significant and could lead to mechanical ventilation.

SUMMARY

This review does not support the use of prophylactic caffeine for preterm infants at high risk of apnoea, bradycardia or hypoxaemic episodes, and concludes that larger studies are required. Caffeine has been shown to be an effective treatment for apnoea in premature neonates, and to prevent the indirect

consequences for neonates having frequent apnoea (such as the need for assisted ventilation). The studies have focussed exclusively on caffeine in the prevention of apnoea in a low-risk population (included in this review) carry a high risk of a type II error. Further studies should assess higher risk infants, and perhaps use a greater dose of caffeine [4]. Caffeine may be used prophylactically to prevent apnoea in preterm infants following general anaesthesia if deemed clinically necessary, but further studies are appropriate to evaluate this treatment in infants at high risk of apnoea, or those that might require mechanical ventilation [5].

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