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Henderson-Smart DJ, Steer PA

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[Intervention Review]

Caffeine versus theophylline for apnea in preterm infants

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ABSTRACT

Background

Recurrent apnea is common in preterm infants, particularly at very early gestational ages. These episodes of loss of effective breathing can lead to hypoxemia and bradycardia, which may be severe enough to require resuscitation including use of positive pressure ventilation. Two forms of methylxanthine (caffeine and theophylline) have been used to stimulate breathing in order to prevent apnea and its consequences.

Objectives

To evaluate the effect of caffeine compared with theophylline treatment on the risk of apnea and use of mechanical ventilation in preterm infants with recurrent apnea.

Search methods

The standard search strategy of the Cochrane Neonatal Review Group was used. This included searches of electronic databases in August 2009: Oxford Database of Perinatal Trials; Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2009); MEDLINE (1966 to April 2009); and EMBASE Drugs and Pharmacology (1990 to April 2009), previous reviews including cross references.

Selection criteria

Randomized and quasi-randomized trials comparing caffeine to theophylline for treating apnea in preterm infants and reporting effects on apnea event rates.

Data collection and analysis

Each author assessed eligibility and trial quality, extracted data separately and compared and resolved differences. Study authors were contacted for additional information.

Main results

Five trials involving a total of 108 infants were included. The quality of most of these small trials was fair to good. No difference in treatment failure rate (less than 50% reduction in apnea/bradycardia) was found between caffeine and theophylline after one to three days treatment (based on two studies) or five to seven days treatment (based on one study). There was no difference in mean apnea rate between caffeine and theophylline groups after one to three days treatment (based on five trials) and five to seven days treatment (based on four trials).

Adverse effects, indicated by tachycardia or feed intolerance leading to change in dosing, were lower in the caffeine group (summary relative risk 0.17, 95% CI 0.04 to 0.72). This was reported and consistent in three studies.

No trial reported the use of ventilation and no data were available to assess effects on growth and development.

Authors' conclusions

Caffeine appears to have similar short-term effects on apnea/bradycardia as does theophylline although caffeine has certain therapeutic advantages over theophylline. Theophylline is associated with higher rates of toxicity. The possibility that higher doses of caffeine might be more effective in extremely preterm infants needs further evaluation in randomized clinical trials.

PLAIN LANGUAGE SUMMARY

Caffeine versus theophylline for apnea in preterm infants

There is some evidence that caffeine is as effective as theophylline in the short-term for reducing apnea in premature babies, is better tolerated and is easier to give.

Apnea is a pause in breathing of greater than 20 seconds. It may occur repeatedly in preterm babies (born before 34 weeks gestation). Persistent apnea may be harmful to the developing brain or organs. Methylxanthines (such as theophylline and caffeine) are drugs that are believed to stimulate breathing efforts and have been used to reduce apnea. This review of trials found that caffeine has similar effects to theophylline but has a larger gap between levels that are therapeutic and those with toxic effects. Caffeine is more easily absorbed and has a longer half-life that allows for once daily dosing.

BACKGROUND

Description of the condition

Infant apnea has been defined as a pause in breathing of greater than 20 seconds or one of less than 20 seconds and associated with bradycardia and/or cyanosis (AAP 2003). Recurrent episodes of apnea are common in preterm infants and the incidence and severity increases at lower gestational ages (Henderson-Smart 1995). Although apnea can occur spontaneously and be attributed to prematurity alone, it can also be provoked or made more severe if there is some additional insult such as infection, hypoxemia or intracranial pathology.

Description of the intervention

Methylxanthines are thought to stimulate breathing efforts and have been used in clinical practice to reduce apnea since the 1970's. Theophylline and caffeine are two forms that have been used. The efficacy of methylxanthines compared with control was evaluated in another review in the Cochrane Library (Henderson-Smart 2004), which concluded that their use reduced apnea. The mechanism of their action is not certain. Possibilities include increased chemoreceptor responsiveness (based on increased breathing responses to CO2), enhanced respiratory muscle performance and generalized central nervous system excitation.

How the intervention might work

Caffeine has a potential therapeutic advantage over theophylline due to its higher therapeutic ratio, more reliable enteral absorption and longer half life, which allows once daily administration (Blanchard 1992).

Why it is important to do this review

If prolonged, apnea can lead to hypoxemia and reflex bradycardia, which may require active resuscitative efforts to reverse. There are clinical concerns that these episodes might be harmful to the developing brain or cause dysfunction of the gut or other organs, although there are no data to support this. Frequent episodes may be accompanied by respiratory failure of sufficient severity as to lead to intubation and the use of intermittent positive pressure ventilation (IPPV).

OBJECTIVES

To evaluate the effect of caffeine compared with theophylline treatment on the risk of apnea and use of mechanical ventilation in preterm infants with recurrent apnea.

Subgroup analyses:

1. Outcomes of different doses of caffeine or theophylline.

2. Outcomes of infants born at different gestational ages or birth weights.

METHODS

Criteria for considering studies for this review

Types of studies

Trials utilising random or quasi-random treatment assignment

Types of participants

Preterm neonates (born before 34 weeks gestation) requiring treatment for recurrent apnea of prematurity.

Types of interventions

Caffeine compared with theophylline for the treatment of apnea of prematurity. Trials in which caffeine and theophylline were compared as prophylactic therapy in preterm infants at risk of developing apnea or those in which they were used to assist extubation following IPPV were not eligible.

Types of outcome measures

Primary outcomes

1. Apnea (failed treatment defined as no clinically important reduction in apnea (>50% reduction), use of IPPV or death during study).
2. Mean rates of apnea

Secondary outcomes

3. Use of IPPV
4. Side effects such as tachycardia or feed intolerance leading to alteration in treatment
5. Longer term growth and development

Search methods for identification of studies

Electronic searches

This included searches of the Oxford Database of Perinatal Trials, Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 2, 2009), MEDLINE (1966 to April 2009), and EMBASE Drugs and Pharmacology (1990 to April 2009) using key words 'caffeine', 'theophylline' and 'apnea', MeSH terms 'infant, preterm', and 'randomized controlled trial' or 'controlled clinical trial'.

Searching other resources

Searches were also made of previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants and journal handsearching mainly in the English language.

Clinical trials registries were also searched for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp)

Data collection and analysis

The standard strategy of the Neonatal Review Group was used.

Selection of studies

All randomized and quasi-randomized controlled trials fulfilling the selection criteria described in the previous section were included. The investigators reviewed the results of the search and separately select the studies for inclusion. The review authors resolved any disagreement by discussion.

Data extraction and management

Data were extracted independently by the two review authors. Any standard error of the mean was replaced by the corresponding standard deviation. Differences were resolved by discussion and

consensus of the reviewers. Where necessary, trial authors were contacted for additional information or data. Information was provided for four of these (Bairam 1987; Fuglsang 1989; Kumar 1992; Scanlon 1992).

Assessment of risk of bias in included studies

The methodological quality of the studies were assessed using the following key criteria: allocation concealment (blinding of randomization), blinding of intervention, completeness of follow-up, and blinding of outcome measurement/assessment. For each criterion, assessment was yes, no, can't tell. Two review authors separately assessed each study. Any disagreement was resolved by discussion. This information was added to the table "Characteristics of Included Studies".

In addition, the following issues were evaluated and entered into the Risk of Bias Table:

1. Sequence generation: Was the allocation sequence adequately generated?

2. Allocation concealment: Was allocation adequately concealed?

3. Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

4. Incomplete outcome data: Were incomplete outcome data adequately addressed?

5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?

6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

Measures of treatment effect

Statistical analyses were performed using Review Manager software. For individual trials, mean differences (and 95% confidence intervals) are reported for continuous variables. For categorical outcomes, the relative risk and risk difference (and 95% confidence intervals) are reported.

Assessment of heterogeneity

We estimated the treatment effects of individual trials and examined heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic.

Data synthesis

For the meta-analysis, weighted mean differences (WMD) and 95% confidence intervals (CI) were reported for continuous variables. For meta-analysis of categorical outcomes the summary relative risks (RR) and risk differences (RD) and 95% CI were calculated using a fixed effects model. To calculate the number needed to treat (NNT) the risk difference (RD) was used.

Subgroup analysis and investigation of heterogeneity

1. Different doses of caffeine or theophylline

2. Infants born at different gestational ages or birth weights.

RESULTS

Description of studies

Results of the search

Nine trials were considered to be potentially eligible for this review.

Included studies

Five studies with a total of 108 preterm infants (54 in each group) were included. Details of the five included studies (Brouard 1985; Bairam 1987; Fuglsang 1989; Scanlon 1992; Kumar 1992) are available in the included table "Characteristics of Included Studies". Brouard 1985; Bairam 1987 and Scanlon 1992 were good quality trials documented in the publications. For the Fuglsang 1989 trial, the author provided study details. Kumar 1992 was only published as an abstract but the author provided missing information about study design and drug dosage.

Excluded studies

Four trials were excluded (Dani 2000; Zanardo 1995; Fang 1998; Laubscher 1998) as no clinical apnea outcome data were available. In addition to the published results, the third and fourth trials had no unpublished data on apnea outcomes (information provided by author Anne Greenough).

Risk of bias in included studies

The overall quality of the included studies was fair/good.

Allocation

Concealment of treatment allocation by blinded randomization was undertaken in three trials (Bairam 1987; Scanlon 1992; Kumar 1992). The method of randomization was not clear in the Brouard 1985 and Fuglsang 1989 trials.

Blinding

Blinding of the intervention outcome assessments was only undertaken in two trials (Bairam 1987; Fuglsang 1989).

Incomplete outcome data

In two trials some of the randomized infants were not analysed because of complications (Scanlon 1992, 8/44 in continuing apnea; Fuglsang 1989, 9/27 in continuing apnea and mean apnea). Despite the high rate of exclusion (30%) in Fuglsang 1989 the baseline information was similar in the two groups of included infants.

Other potential sources of bias

None known.

Effects of interventions

Caffeine vs. theophylline for apnea in preterm infants (all infants)(Comparison 1):

There is no difference in the failure rate (< 50% reduction in apnea/bradycardia) of treatment with caffeine or theophylline at one to three days [two studies, Bairam 1987; Scanlon 1992); summary relative risk (RR) 1.35, 95% confidence interval (CI) 0.41, 4.52] (*Outcome 1.1*) or at five to seven days (one study, Bairam 1987; RR 1.50, 95% CI 0.32, 7.14) (*Outcome 1.2*). There was a small borderline but insignificant increase in the mean rate/100 min of

apnea in the caffeine group at one to three days [all five included studies, weighted mean difference (WMD) 0.11, 95% CI 0.00, 0.22] (*Outcome 1.3*). In individual studies at one to three days there was a significantly higher mean apnea rate in the caffeine group in Scanlon 1992 (0.46 95%CI 0.14, 0.78) and a non-significant trend of increase in Bairam 1987. At five to seven days there was no difference in mean apnea rates in individual studies or in WMD between groups [four studies, Bairam 1987; Brouard 1985; Fuglsang 1989; Kumar 1992; (WMD 0.0; 95% CI -0.05, 0.05] (*Outcome 1.4*), or in individual studies.

Side effects, as indicated by tachycardia or feed intolerance leading to change in dosing, were lower in the caffeine group [RR 0.17; 95% CI 0.04, 0.72; risk difference (RD) -0.29; 95% CI -0.47, -0.10, number needed to treat (NNT) 3.5; 95% CI 2.1, 9.6] (*Outcome 1.5*). This was consistent across the three studies reporting side effects data (Bairam 1987; Brouard 1985; Scanlon 1992).

No trial reported the use of IPPV and no data are available to assess the effects on growth and neurological development.

There was insufficient data to undergo subgroup analyses of outcomes of different doses of caffeine or theophylline or outcomes of infants born at different gestational ages or birth weights.

DISCUSSION

Summary of main results

There was no difference in the failure rate (number of infants with < 50% reduction in apnea) between caffeine and theophylline at one to three and five to seven days. There was also no significant differences in the weighted mean differences of apnea on day one to day three and on day five to day seven.

Three studies found standard caffeine treatment to have less short-term side effects than theophylline, consistent with known caffeine and theophylline pharmacology. The NNT of 3.5 indicates that for every three to four patients treated with caffeine, one patient having a significant adverse event can be avoided.

There are no data from these studies on long-term effectiveness.

Overall completeness and applicability of evidence

There is a need for clinical trials with larger numbers of infants born at a lower gestational age to demonstrate the effectiveness and safety of caffeine compared to theophylline treatment with respect to clinically important outcomes including safety and long-term effects on neurodevelopmental outcome. The appropriate dose of methylxanthine therapy requires further investigation.

The daily maintenance dose of caffeine was 2.5 mg (equal to 5 mg caffeine citrate) in four trials and 3 mg (10 mg caffeine citrate) in one (Scanlon 1992). In most clinical practices, 5 mg (10 mg caffeine citrate) is used. The possibility that higher doses of caffeine might be more effective in extremely preterm infants needs further evaluation in randomized clinical trials.

Quality of the evidence

The results of this review should be interpreted with caution. The number of infants in each study was small. There was some variability in the characteristics of participants in terms of gestational age as well as clinical status. For example Scanlon 1992 examined infants who were of lower gestational age and who were oxygen dependent. This trial contributed the most weight to the difference in mean rates of apnea/bradycardia at one to three days. It also examined a third treatment arm of higher dose caffeine but this has not been included here.

AUTHORS' CONCLUSIONS

Implications for practice

In treatment of preterm infants with apnea, caffeine appears to have similar short-term reductions of apnea/bradycardia when compared to theophylline. In view of the other therapeutic advantages of caffeine (a higher therapeutic ratio, more reliable enteral absorption and a longer half life as well as less side effects than theophylline) caffeine is the preferred treatment for apnea in preterm infants. There are no data from these studies on the long-term effectiveness and safety of the drugs.

Implications for research

There is a need for clinical trials with larger numbers of infants born at lower gestation to demonstrate the effectiveness and safety of caffeine compared to theophylline treatment with respect to clinically important outcomes including safety and longterm effects on neurodevelopmental outcome. The appropriate dose of methylxanthine therapy requires further investigation.

The possibility that higher doses of caffeine might be more effective in extremely preterm infants needs further evaluation in randomized clinical trials.

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Brouard 1985 *{published data only}*

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Fuglsang 1989 *{published data only}*

Fuglsang G, Nielsen K, Kjaer Nielsen L, Sennels F, Jakobsen P, Thelle T. The effect of caffeine compared with theophylline in the treatment of idiopathic apnea in premature infants. *Acta Paediatrica Scandinavica* 1989;**78**:786-8.

Kumar 1992 *{published and unpublished data}*

Kumar SP, Mehta PN, Bradley BS, Ezhuthachan SG. Documented monitoring (DM) shows theophylline (T) to be more effective than caffeine (C) in prematurity apnea (PA). *Pediatric Research* 1992;**31**:208A.

Scanlon 1992 *{published and unpublished data}*

Scanlon JE, Chin KC, Morgan ME, Durbin GM, Hale KA, Brown SS. Caffeine or theophylline for neonatal apnoea?. *Archives of Disease in Childhood* 1992;**67**:425-8.

References to studies excluded from this review

Dani 2000 *{published data only}*

Dani C, Bertini G, Reali M, Tronchin M, Wiechmann L, Martelli E, Rubaltelli F. Brain hemodynamic changes in preterm infants after maintenance dose caffeine and aminophylline treatment. *Biology of the Neonate* 2000;**78**:27-32.

Fang 1998 *{published data only}*

Fang S, Sherwood R, Gamsu H, Marsden J, Peters T, Greenough A. Comparison of the effects of theophylline and caffeine on serum erythropoietin concentration in premature infants. *European Journal of Pediatrics* 1998;**157**:406-9.

Laubscher 1998 *{published data only}*

Laubscher B, Greenough A, Dimitriou G. Camparative effects of theophylline and caffeine on respiratory function of prematurely born infants. *Early Human Development* 1998;**50**:185-92.

Sims 1989 *{published data only}*

Sims ME, Rangasamy R, Lee S, Chung H, Cohen J, Walther FJ. Comparative evaluation of caffeine and theophylline for weaning premature infants from the ventilator. *American Journal of Perinatology* 1989;**6**:72-5.

Zanardo 1995 *{published data only}*

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References to other published versions of this review

Steer 1998

Steer P, Henderson-Smart D. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database of Systematic Reviews* 1998, Issue 2. [DOI: 10.1002/14651858]

Steer 2003

Steer P, Henderson-Smart D. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bairam 1987

Methods	Single centre Blinding of randomization - yes in sealed envelopes Blinding of intervention - yes Complete followup - yes * Blinding of outcome measure - yes *extra information provided by the author (personal correspondence)
Participants	20 preterm infants (mean gestational age 30 weeks) included after 24 hour recording documented ≥ 3 apneas
Interventions	Exp: standard caffeine = loading dose 10 mg/kg, maintenance dose 1.25 mg/kg/12hrs Control: theophylline = loading dose 6 mg/kg, maintenance dose 2 mg/kg/12hrs
Outcomes	Frequency of apnea, bradycardia, apnea with bradycardia, systolic arterial pressure, tachycardia, weight gain, gastrointestinal intolerance, behavioural assessment (scaled-score of motor activity, reactivity and sucking).
Notes	Apnea defined as cessation of breathing of 15 seconds or more, or apnea plus bradycardia (<100). Author communication indicated that these were collected separately and in the review they were combined for primary outcome measure.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Both interventions and outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All studied
Selective reporting (reporting bias)	Low risk	None selected
Other bias	High risk	Assisted by author correspondence

Brouard 1985

Methods	Single centre Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - yes Blinding of outcome measure - can't tell
Participants	16 preterm infants (mean gestational age 30 weeks) enrolled infants where ≥ 3 severe apneas noted per 24 hours

Brouard 1985 *(Continued)*

Interventions	Exp: standard caffeine = loading dose 10 mg/kg intramuscularly, daily maintenance dose 2.5 mg/kg orally to target serum level of 8 - 16 mg/l) Control: Aminophylline used as theophylline = loading dose 5.5 mg/kg intravenously, maintenance dose adjusted to maintain plasma levels at 5 - 10 mg/kg
Outcomes	Apnea frequency on day 0, 1, and 5 Tachycardia Weight
Notes	Severe apnea defined as cessation of breathing for 10 secs with heart rate < 80 for > 30 seconds or <60 for > 15 seconds

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of interventions, blinding of outcome assessments unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	All studied
Selective reporting (reporting bias)	Low risk	No selective cases reported
Other bias	Unclear risk	None stated

Fuglsang 1989

Methods	Single centre Blinding of randomization - uncertain Blinding of intervention - yes Complete followup - no; 9 of the 27 randomized infants were excluded by day 5 because they had causes (6 with septicemia and need for assisted ventilation, 2 with cerebral hemorrhage) and 1 withdrawn by parents. Blinding of outcome measure - yes, continuous polygraph research recording while treatment blinded.
Participants	Data were reported for 18 preterm infants with idiopathic apnea requiring treatment. Mean (SD) comparisons between groups; weeks of gestational age at birth 31 (3) in the caffeine group and 30 (2) in the theophylline group; birth weight 1499 (467) grams and 1351 (489) respectively, age in days at randomization 8 (11) and 7 (13).
Interventions	Caffeine citrate 20 mg/kg loading dose and maintenance dose of 5 mg/kg once daily Aminophylline used as theophylline 7.5 mg/kg loading dose and maintenance dose of 3.75 mg/kg 12 hourly. Ethylenediamine salt of theophylline (=aminophylline) was used. Both drugs were given orally.
Outcomes	Apnea - cessation of breathing for more than 20 secs. In the paper the results were in a graph. The author provided us with a table of daily mean and SD of apnea per 24 hours for each group. Rates on day 2

Fuglsang 1989 *(Continued)*

	(middle of 1-3) and day 6 (middle of 5-7) were used and converted to rates of apnea/100mins as in other studies. Bradycardia - heart rate below 100 beats/min - data not reported in the paper Side effects - raised mean heart rate, excessive central nervous system stimulation or dyspepsia. These were not reported as individual data but verbal comments in the text of the paper indicated there was no side effects in either group.
Notes	In the first publication of this review and in updates this trial remained excluded because of the large proportion of infants excluded (9). The author provided valuable information and the baseline comparison of the remaining two groups (9 infants in each) was similar.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of interventions and outcome assessments - stated in paper and from author
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 of the 27 randomized infants were excluded by day 5 because they had causes (6 with septicemia and need for assisted ventilation, 2 with cerebral hemorrhage) and 1 withdrawn by parents
Selective reporting (reporting bias)	High risk	As stated above in incomplete outcome data addressed
Other bias	Unclear risk	Not stated

Kumar 1992

Methods	Single centre Randomization - yes, undertaken in the pharmacy with sealed envelopes Blinding of intervention - no Completenes of follow up - unknown Blindness of outcome assessment - unknown
Participants	24 preterm infants with recurrent apnea, 11 allocated to caffeine and 13 to theophylline
Interventions	Caffeine citrate 20 mgs/kg loading dose, 5 mg/kg/24 hrs maintenance Theophylline 5.5 mg/kg loading dose, 1.1 mg/kg 6 hrly maintenance
Outcomes	Days 1, 3 and 7 Apnea ≥ 15 sec / 12 hr Bradycardia < 80 / 12 hrs SaO2 < 85 / 12 hrs

Kumar 1992 *(Continued)*

Notes	Only published as an abstract but additional information regarding randomisation methods and dosages of caffeine and theophylline provided by author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Randomization - yes, undertaken in pharmacy with sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of interventions or outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	High risk	Comment from author
Other bias	Low risk	Only published as abstract but additional information given by author

Scanlon 1992

Methods	Single centre Blinding of randomization - yes Blinding of intervention - no Complete followup - no success rates (>50% reduction in apnea) 4 infants on caffeine and 2 infants on theophylline were excluded from analysis because of a defined cause of apnea - septicaemia, neurological abnormality or oesophageal reflux. All were examined for mean rates of apnea Blinding of outcome measure - no
Participants	30 preterm infants <31 week gestation with apnea (≥ 10 in 8 hours or 4 in 1 hour)
Interventions	Exp: standard caffeine = loading dose 12.5 mg/kg and maintenance 3 mg/kg/24 hours Control : theophylline = loading dose 7.5 mg/kg/8hrs (aiming for plasma levels of 13 - 20 mg/l) There was also a group that received higher dose caffeine, 25mg/kg load and 6 mg/kg/24 hrs, maintenance which is not included in this review.
Outcomes	Apnea frequency over 24 hours reported after one day and after 2 days Number of infants with > 50 % reduction in apnea frequency (12 in caffeine group and 14 in theophylline group)
Notes	Apnea defined as a decrease in heart rate of 40 beats per minute with cessation of breathing and requiring stimulation

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate

Scanlon 1992 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Interventions and outcomes not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All examined
Selective reporting (reporting bias)	Low risk	No selective reporting
Other bias	Low risk	None in publication

Characteristics of excluded studies *[ordered by study ID]*

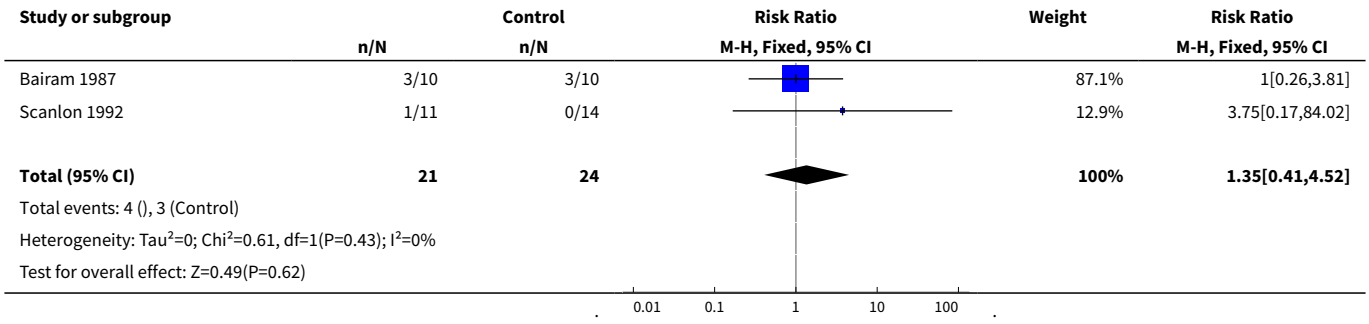
Study	Reason for exclusion
Dani 2000	No clinical outcome data available
Fang 1998	No outcome data on apnea is available
Laubscher 1998	No outcome data on apnea is available
Sims 1989	For weaning premature infants from the ventilator, not treatment for apnea
Zanardo 1995	No clinical outcome data available

DATA AND ANALYSES

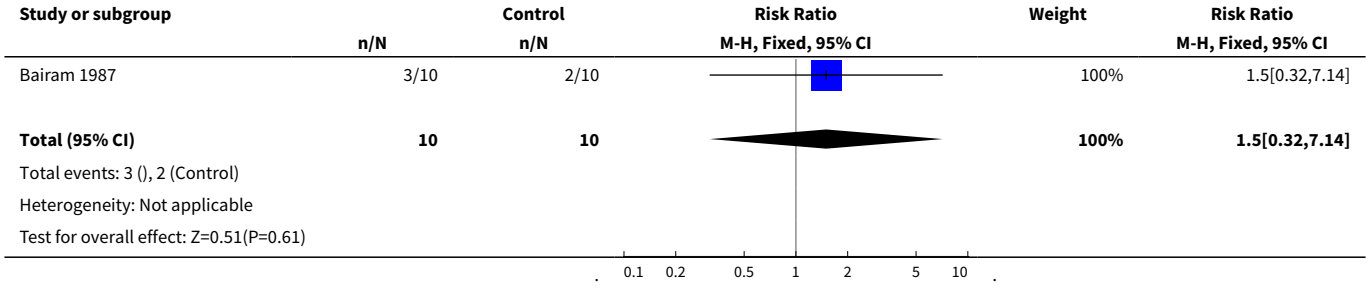
Comparison 1. Caffeine vs. theophylline for apnea in preterm infants (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Continuing apnea at 1-3 days	2	45	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.41, 4.52]
2 Continuing apnea at 5-7 days	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.32, 7.14]
3 Mean apnea rate /100 mins at 1-3 days	5	108	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.00, 0.22]
4 Mean apnea rate /100 mins at 5-7 days	4	78	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.05, 0.05]
5 Side effects	3	66	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.04, 0.72]

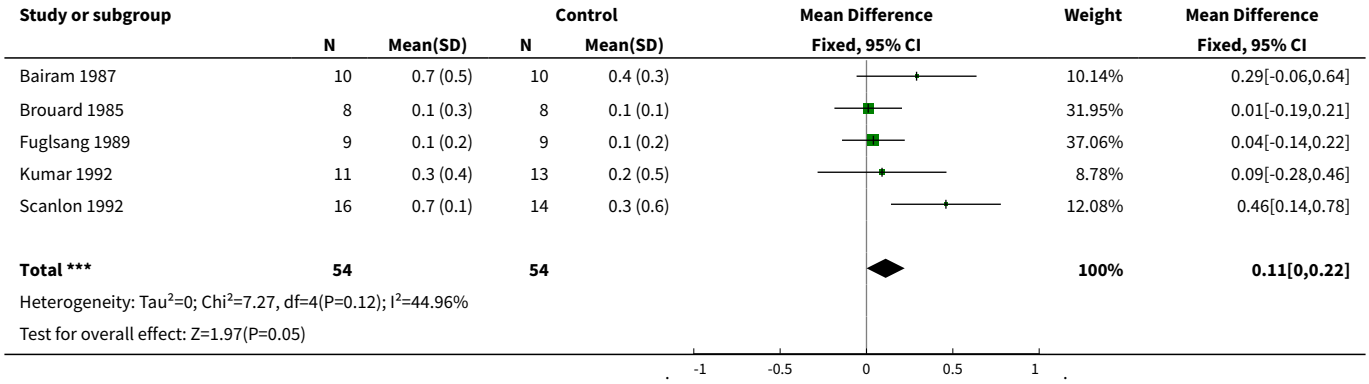
Analysis 1.1. Comparison 1 Caffeine vs. theophylline for apnea in preterm infants (all infants), Outcome 1 Continuing apnea at 1-3 days.



Analysis 1.2. Comparison 1 Caffeine vs. theophylline for apnea in preterm infants (all infants), Outcome 2 Continuing apnea at 5-7 days.

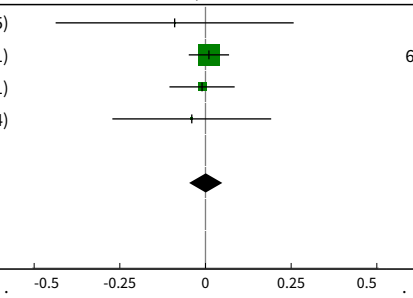


Analysis 1.3. Comparison 1 Caffeine vs. theophylline for apnea in preterm infants (all infants), Outcome 3 Mean apnea rate /100 mins at 1-3 days.



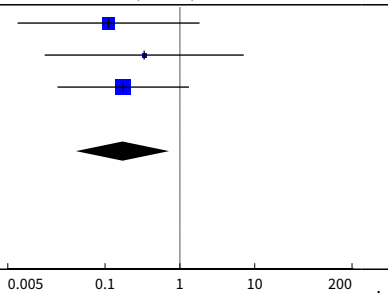
Analysis 1.4. Comparison 1 Caffeine vs. theophylline for apnea in preterm infants (all infants), Outcome 4 Mean apnea rate /100 mins at 5-7 days.

Study or subgroup			Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bairam 1987	10	0.3 (0.3)	10	0.3 (0.5)		1.94%	-0.09[-0.44,0.26]
Brouard 1985	8	0.1 (0.1)	8	0.1 (0.1)		67.79%	0.01[-0.05,0.07]
Fuglsang 1989	9	0 (0)	9	0 (0.1)		25.9%	-0.01[-0.11,0.09]
Kumar 1992	11	0.2 (0.2)	13	0.2 (0.4)		4.36%	-0.04[-0.27,0.19]
Total ***	**38**		**40**			**100%**	**0[-0.05,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.53, df=3(P=0.91); I^2=0%							
Test for overall effect: Z=0.03(P=0.98)							



Analysis 1.5. Comparison 1 Caffeine vs. theophylline for apnea in preterm infants (all infants), Outcome 5 Side effects.

Study or subgroup		Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Bairam 1987	0/10	4/10		39.71%	0.11[0.01,1.83]
Brouard 1985	0/8	1/8		13.24%	0.33[0.02,7.14]
Scanlon 1992	1/16	5/14		47.06%	0.18[0.02,1.32]
Total (95% CI)	**34**	**32**		**100%**	**0.17[0.04,0.72]**
Total events: 1 (), 10 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=2(P=0.87); I^2=0%					
Test for overall effect: Z=2.42(P=0.02)					



WHAT'S NEW

Date	Event	Description
25 February 2013	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 2, 1998

Date	Event	Description
16 April 2012	Amended	Change of contact person only.
7 December 2010	Amended	Contact details updated.

Date	Event	Description
5 November 2009	New citation required but conclusions have not changed	Two new trials included; no change to conclusions.
17 August 2009	New search has been performed	This review updates the review "Caffeine versus theophylline for apnea in preterm infants", published in the Cochrane Database of Systematic Reviews, Issue 1, 2003 (Steer 2003). Updated search August 2009 identified two new trials for inclusion. No change to conclusions.
14 October 2002	New search has been performed	This review is an update of the existing review: Steer P, Henderson-Smart D. "Caffeine versus theophylline for apnea in preterm infants" published in The Cochrane Library, Issue 2, 1998. In an updated and extended search to October 2002, four potentially eligible studies were identified: two were excluded (Dani, Zanardo) and two are awaiting assessment (Fang, Laubscher). This update does not include any new studies.
13 February 1998	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

The two review authors contributed equally to the review process and independently accessed trials for eligibility, trial quality, and performed data extraction. This updated was performed by Henderson-Smart and approved by Steer.

DECLARATIONS OF INTEREST

Review authors Steer and Henderson-Smart, were investigators in a trial of caffeine in preterm infants: "High dose caffeine for extubation of preterm Infants: a randomised controlled trial."

SOURCES OF SUPPORT

Internal sources

- Pediatrics, McMaster Children's Hospital, Hamilton, Ontario, Canada.
- NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.
- School of Medicine, Faculty of Health Sciences, University of Queensland, Brisbane, Australia.

External sources

- Department of Health and Ageing, Commonwealth Government, Canberra ACT, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Apnea [*drug therapy]; Bronchodilator Agents [*therapeutic use]; Caffeine [*therapeutic use]; Central Nervous System Stimulants [*therapeutic use]; Infant, Premature; Infant, Premature, Diseases [*drug therapy]; Randomized Controlled Trials as Topic; Theophylline [*therapeutic use]

MeSH check words

Humans; Infant, Newborn