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# Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants (Review)

Subramaniam P, Ho JJ, Davis PG

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[Intervention Review]

# Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

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## ABSTRACT

### Background

Cohort studies have suggested that nasal continuous positive airways pressure (CPAP) starting in the immediate postnatal period before the onset of respiratory disease (prophylactic CPAP) may be beneficial in reducing the need for intubation and intermittent positive pressure ventilation (IPPV) and in preventing bronchopulmonary dysplasia (BPD) in preterm or low birth weight infants.

### Objectives

To determine if prophylactic nasal CPAP started soon after birth regardless of respiratory status in the very preterm or very low birth weight infant reduces the use of IPPV and the incidence of bronchopulmonary dysplasia (BPD) without adverse effects.

### Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 1), MEDLINE via PubMed (1966 to 31 January 2016), EMBASE (1980 to 31 January 2016), and CINAHL (1982 to 31 January 2016). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

### Selection criteria

All trials using random or quasi-random patient allocation of very preterm infants (under 32 weeks' gestation) or less than 1500 grams at birth were eligible. We included trials if they compared prophylactic nasal CPAP started soon after birth regardless of the respiratory status of the infant with 'standard' methods of treatment such as IPPV, oxygen therapy or supportive treatment. We excluded studies where prophylactic CPAP was compared with CPAP along with other interventions.

### Data collection and analysis

We used the standard methods of Cochrane and its Neonatal Review Group, including independent study selection, assessment of trial quality and extraction of data by two authors. Data were analysed using risk ratio (RR) and the meta-analysis was performed using a fixed-effect model.


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**Main results**

Seven trials recruiting 3123 babies were included in the meta-analysis. Four trials recruiting 765 babies compared CPAP with supportive care and three trials (2364 infants) compared CPAP with mechanical ventilation. Apart from a lack of blinding of the intervention all studies were of low risk of bias.

In the comparison of CPAP with supportive care there was a reduction in failed treatment (typical risk ratio (RR) 0.66, 95% confidence interval (CI) 0.45 to 0.98; typical risk difference (RD) −0.16, 95% CI −0.34 to 0.02; 4 studies, 765 infants, very low quality evidence). There was no reduction in bronchopulmonary dysplasia (BPD) or mortality.

In trials comparing CPAP with assisted ventilation with or without surfactant, CPAP resulted in a small but clinically significant reduction in the incidence of BPD at 36 weeks, (typical RR 0.89, 95% CI 0.79 to 0.99; typical RD −0.04, 95% CI −0.08 to 0.00; 3 studies, 772 infants, moderate-quality evidence); and death or BPD (typical RR 0.89, 95% CI 0.81 to 0.97; typical RD −0.05, 95% CI −0.09 to 0.01; 3 studies, 1042 infants, moderate-quality evidence). There was also a clinically important reduction in the need for mechanical ventilation (typical RR 0.50, 95% CI 0.42 to 0.59; typical RD −0.49, 95% CI −0.59 to −0.39; 2 studies, 760 infants, moderate-quality evidence); and the use of surfactant in the CPAP group (typical RR 0.54, 95% CI 0.40 to 0.73; typical RD −0.41, 95% CI −0.54 to −0.28; 3 studies, 1744 infants, moderate-quality evidence).

**Authors' conclusions**

There is insufficient evidence to evaluate prophylactic CPAP compared to oxygen therapy and other supportive care. However when compared to mechanical ventilation prophylactic nasal CPAP in very preterm infants reduces the need for mechanical ventilation and surfactant and also reduces the incidence of BPD and death or BPD.

## PLAIN LANGUAGE SUMMARY

**Nasal continuous positive airways pressure started immediately after birth for preventing illness and death in very preterm infants**

**Review Question**: If CPAP were started immediately after birth before the onset of respiratory distress would it reduce the need for mechanical ventilation and would it reduce bronchopulmonary dysplasia (BPD)?

**Background:** Preterm babies may have breathing difficulty due to immature lungs, a condition known as Respiratory Distress Syndrome (RDS).The usual treatment is to assist their breathing with the help of a mechanical ventilator. Recent studies have shown that these babies are further helped by instilling surfactant into the 'breathing tube' while giving support with mechanical ventilation. However using a mechanical ventilator has its own dangers, the most important being BPD, a form of lung damage that occurs when preterm lungs are exposed to mechanical ventilation. Nasal continuous positive airway pressure (nasal CPAP) is a form of respiratory support delivered either via tubes inserted into the nostrils or a mask placed over the nose, leaving the mouth free. It is designed to ease the breathing effort of babies who can breathe on their own and has been found to help preterm babies if it is used to treat established RDS.

**Search Date:** The evidence is current to January 2016.

**Study Characteristics:** Randomised controlled trials of preterm babies below 32 weeks' gestation or below 1500 grams at birth who were treated with CPAP applied within the first 15 minutes of life compared with babies who were given either (1) routine supportive care such as oxygen therapy or (2) mechanical ventilation.

**Results:** There were a total of seven studies involving 3123 infants. They were generally of moderate quality. Parents and care-givers would have known which treatment group the babies were in, but we judged this not to be important for most outcomes measured. In the four studies (765 babies) comparing CPAP with supportive care, CPAP resulted in fewer infants requiring further breathing assistance but there was considerable inconsistency between the studies. In the three studies (2354 babies) that compared CPAP with assisted ventilation with or without surfactant, CPAP resulted in a small but clinically important reduction in BPD and the combined outcome of BPD and mortality. There was a reduction in the need for mechanical ventilation and the use of surfactant in the CPAP group.


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## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

**Prophylactic CPAP compared to supportive care for preventing morbidity and mortality in very preterm infants**

**Patient or population:** patients with preventing morbidity and mortality in very preterm infants
**Settings:** NICUs in high and middle income countries
**Intervention:** Prophylactic CPAP
**Comparison:** Supportive care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Supportive care | Prophylactic CPAP | | | | |
| **Failed Treatment** | **Study population** | | **RR 0.66** (0.45 to 0.98) | 765 (4 studies) | ⊕○○○ **very low**[1,2,3] | Outcome subjective and may be susceptible to lack of blinding |
| | **392 per 1000** | **258 per 1000** (176 to 384) | | | | |
| **Bronchopulmonary dysplasia at 36 weeks** Oxygen dependency at 36 weeks' post-menstrual age | **Study population** | | **RR 0.79** (0.5 to 1.24) | 683 (3 studies) | ⊕⊕⊕○ **moderate**[3] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding |
| | **124 per 1000** | **98 per 1000** (62 to 154) | | | | |
| | **Moderate** | | | | | |
| | **152 per 1000** | **120 per 1000** (76 to 188) | | | | |
| **Neonatal death** Mortality at any time | **Study population** | | **RR 1.04** (0.56 to 1.93) | 765 (4 studies) | ⊕⊕⊕○ **moderate**[3] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | **50 per 1000** | **52 per 1000** (28 to 97) | | | | |
| | **Moderate** | | | | | |
| | **44 per 1000** | **46 per 1000** (25 to 85) | | | | |
| **Death or bronchopulmonary dysplasia** Neonatal death at any time or oxygen dependency at 36 weeks' post-menstrual age | **Study population** | | **RR 0.7** (0.41 to 1.21) | 256 (1 study) | ⊕⊕⊕◯ **moderate**[3] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding |
| | **192 per 1000** | **134 per 1000** (79 to 232) | | | | |
| **Pneumothorax** Any air leak or pneumothorax | **Study population** | | **RR 0.75** (0.34 to 1.63) | 568 (3 studies) | ⊕⊕⊕◯ **moderate**[3] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding |
| | 50 per 1000 | 38 per 1000 (18 to 82) | | | | |
| **IVH grade 3 or 4** | **Study population** | | **RR 1.02** (0.3 to 3.46) | 486 (2 studies) | ⊕⊕⊕◯ **moderate**[3] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding |
| | **38 per 1000** | **38 per 1000** (11 to 130) | | | | |
| **Neurodevelopmental outcome** | No study reported this outcome | | | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is taken from the pooled estimates of the included studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Downgraded one level for serious study limitations due to no blinding of intervention or outcome assessment
[2] Downgraded one level for serious inconsistency due to considerable unexplained heterogeneity across included studies ($I^2$ = 70%)
[3] Downgraded one level due to serious imprecision because the 95% confidence interval includes both appreciable benefit and harm/appreciable harm


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# BACKGROUND

## Description of the condition

Respiratory distress syndrome (RDS) is the most common respiratory disorder of premature infants especially for those below 35 weeks' gestation although older infants with delayed lung maturation of different etiologies can also be afflicted. In RDS the structurally immature, surfactant-deficient lung has a tendency to collapse. Although the poorly ventilated areas may be relatively well perfused this can result in the typical ventilation-perfusion mismatch leading to hypoxia and hypercarbia. If severe enough there may be pulmonary vasoconstriction leading to persistent pulmonary hypertension and left-to-right ductal shunting leading to more severe hypoxia. Histologically RDS is characterised by leakage of proteinaceous fluid into the alveoli and hyaline membrane formation (Rodriguez 2002).

## Description of the intervention

In the early days of neonatal intensive care the only available treatments for RDS were supportive, such as provision of warmth, fluid, calories and oxygen. Two major categories of respiratory support became available in the 1960s and 1970s: mechanical ventilation via an endotracheal tube and continuous positive airway pressure (CPAP). Both could be given prophylactically to infants at risk of developing RDS or as rescue therapy to infants with signs of respiratory failure (Polin 2002). Subsequently two effective perinatal interventions - surfactant administration, administered via an endotracheal tube (Seger 2009; Soll 1998a; Soll 1998b); and antenatal corticosteroids (Roberts 2006) - were evaluated and incorporated into standard care.

Nasal CPAP is a noninvasive method for applying a constant distending pressure to the lungs via the nostrils during inhalation and exhalation to support spontaneously breathing newborn infants with lung disease. The clinical goals of CPAP are to maintain the functional residual capacity of the lungs and support gas exchange. This reduces apnoea, work of breathing, and lung injury. CPAP is most commonly delivered to the nasal airway opening using binasal short prongs or a nasal mask. Pressure is generated using a variety of devices. CPAP is generally well tolerated, in part because infants are preferential or "obligatory nasal-breathers" (Kattwinkel 1973).

CPAP is an attractive option for supporting neonates with respiratory distress, because it preserves spontaneous breathing, does not require endotracheal intubation, and may result in less lung injury than mechanical ventilation (Sweet 2007). Cohort studies of variations in practice between centres have suggested that early nasal CPAP may be beneficial in reducing the need for intubation for intermittent positive pressure ventilation (IPPV) and the incidence of bronchopulmonary dysplasia (BPD) (Avery 1987; Jonsson 1997). Therefore CPAP needs to be compared with both supportive care and mechanical ventilation.

Cohort studies using historical controls have suggested that prophylactic nasal CPAP initiated immediately after birth regardless of respiratory status in very low birth weight (VLBW) infants is effective in reducing the need for IPPV without worsening other measures of neonatal outcome (Gittermann 1997; Jacobsen 1993). In these studies no significant decrease in the incidence of BPD was found with elective CPAP.

## How the intervention might work

Nasal CPAP has been adopted by many NICUs as a way of reducing rates of bronchopulmonary dysplasia in premature neonates, but assessment of its benefits is complicated by questions about the simultaneous effects of concomitant surfactant treatment and other NICU interventions (Patel 2008).

CPAP prevents end-alveolar collapse, reduces the work of breathing and decreases ventilation-perfusion mismatch and may reduce adverse effects of mechanical ventilation (Rodriguez 2002).

CPAP might not work as well in less mature babies, such as those below 28 weeks' gestation whose lungs are less developed and who are more prone to apnoea and respiratory failure (Gerber 2012); and it might work better if given simultaneously with surfactant (Stevens 2008).

A feasibility pilot study by the NIH network, in which early CPAP in the delivery room was used for infants less than 28 weeks' gestational age, showed that while nasal CPAP could be initiated early only 20% of infants did not need intubation during the seven days after birth (Finer 2010).

## Why it is important to do this review

There are several problems interpreting these observational studies. Comparisons between centres and between infants in different eras are confounded by variations in the characteristics of infants entering treatment programmes, such as the gestational age of cohorts based on birth weight (Avery 1987); and in co-interventions such as antenatal steroid administration (Gittermann 1997). Furthermore, the definition of the major end-point (failed CPAP) varies. The general approach towards intubation is often more 'restrictive' in centres which use the policy of elective CPAP as part of a package of minimal intervention and 'permissive hypercarbia'.

Randomised controlled trials are required to minimise bias and give a more precise measure of the effectiveness of prophylactic nasal CPAP (Lundstrom 1996). Bancalari 1992 carried out an earlier systematic review of this subject.

Cochrane reviews have described a variety of uses of CPAP for the neonate. These include: CPAP compared with theophylline for apnoea prematurity (Henderson-Smart 2001); CPAP compared with nasal intermittent positive pressure ventilation (Lemyre 2002);


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CPAP for respiratory distress (Ho 2010; Ho 2015); CPAP to reduce extubation failure after mechanical ventilation (Davis 2003); and CPAP compared with high flow nasal cannula (Wilkinson 2011). An existing review describes the use of surfactant during the course of CPAP (INtubate-SURfactant administration and Extubate to nasal continuous positive airway pressure (INSURE)) (Stevens 2008).

This review looks at the routine use of CPAP prior to the onset of respiratory disease and compares it with other forms of treatment.

# OBJECTIVES

To determine if prophylactic nasal CPAP started soon after birth regardless of respiratory status in the very preterm or very low birth weight infant reduces the use of IPPV and the incidence of bronchopulmonary dysplasia (BPD) without adverse effects.

# METHODS

## Criteria for considering studies for this review

### Types of studies

All trials using random or quasi-random patient allocation were eligible.

### Types of participants

Very preterm infants below 32 weeks' gestation or less than 1500 grams at birth regardless of respiratory status. We included studies where at least 80% meet these criteria.

### Types of interventions

Prophylactic nasal CPAP starting within 5 to 15 minutes of life regardless of the respiratory status of the infant compared with other forms of treatment. For previous versions of this review we included only one comparison (CPAP versus standard care). For this update we made a decision to include a second comparison (CPAP versus assisted ventilation) and we have discontinued the use of the term 'standard care' in preference for the term 'supportive care'.

1. CPAP started soon after birth compared to supportive care which may include supplemental oxygen delivered by head box or standard nasal canula.
2. CPAP compared to assisted ventilation with or without surfactant started within the first 15 minutes of life usually in the delivery room.

Trials in which nasal CPAP was used early in the treatment of the respiratory distress syndrome were not eligible for this review and these are considered in other reviews (Ho 2010; Ho 2015).

We excluded trials where CPAP was used along with surfactant administration followed by a brief period of mechanical ventilation. This is addressed in another review (Stevens 2008).

### Types of outcome measures

The main measures of the response to treatment sought in this review were a reduction in the use of IPPV and in the incidence of bronchopulmonary dysplasia (BPD).

**Outcomes nominated a priori**

#### Primary outcomes

For Comparison 1: CPAP started soon after birth compared to supportive care which may include supplemental oxygen delivered by head box or standard nasal canula.

1. Failure of treatment as indicated by recurrent apnoea, hypoxia, hypercarbia (such as $PaCO_2$ > 60 mmHg) and increasing oxygen requirement or the need for mechanical ventilation
2. Rate of BPD; a) oxygen therapy at 28 days with or without an abnormal chest X-ray; b) oxygen therapy at 36 weeks' postmenstrual age
3. Mortality to latest follow-up
4. Combined outcome of BPD and mortality

For Comparison 2: CPAP compared to assisted ventilation with or without surfactant started within the first 15 minutes of life usually in the delivery room.

1. BPD
2. Mortality at any time
3. Combined outcome of BPD and mortality
4. Assisted ventilation

#### Secondary outcomes

1. Use of surfactant
2. Pulmonary air leaks (pneumothorax, pneumomediastinum)
3. Local trauma (nasal injury, subglottic stenosis, laryngeal injury)
4. Feed intolerance (days to full feeds)
5. Rate of intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL)
6. Necrotizing enterocolitis (proven by radiology or at surgery)
7. Rate of late onset systemic infection
8. Retinopathy of prematurity (ROP)
9. Use of health care resources/costs of care/length of stay
10. Neurodevelopmental status at follow-up: neurodevelopment measured on a validated scale that measures cognitive, motor, behavioural function, or blindness, deafness, or cerebral palsy at about 2 years of age.


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## Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register).

### Electronic searches

We conducted a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 1) in *The Cochrane Library*; MEDLINE via PubMed (1996 to 31 January 2016); EMBASE (1980 to 31 January 2016); and CINAHL (1982 to 31 January 2016). We used the following search terms: (respiratory distress syndrome OR hyaline membrane disease OR continuous distending pressure OR continuous distending airway pressure OR continuous positive airway pressure OR continuous positive transpulmonary pressure OR continuous transpulmonary pressure OR continuous inflating pressure OR continuous negative distending pressure OR continuous negative pressure OR continuous airway pressure OR CPAP), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We did not apply language restrictions.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform www.whoint/ictrp/search/en/; and the ISRCTN Registry).

### Searching other resources

We searched previous reviews including cross-references, abstracts, conference or symposia proceedings, expert informants, and journal handsearching mainly in the English language. Abstracts of the American Society for Pediatric Research were handsearched from 1996 to 2014 inclusive.

## Data collection and analysis

### Selection of studies

We used the standard review methods of the Cochrane Neonatal Review Group. Two people (PS and JJH) independently screened the search results. The three review authors (PS, JJH, PD) assessed for inclusion in the review all abstracts and published studies identified as potentially relevant by the literature search.

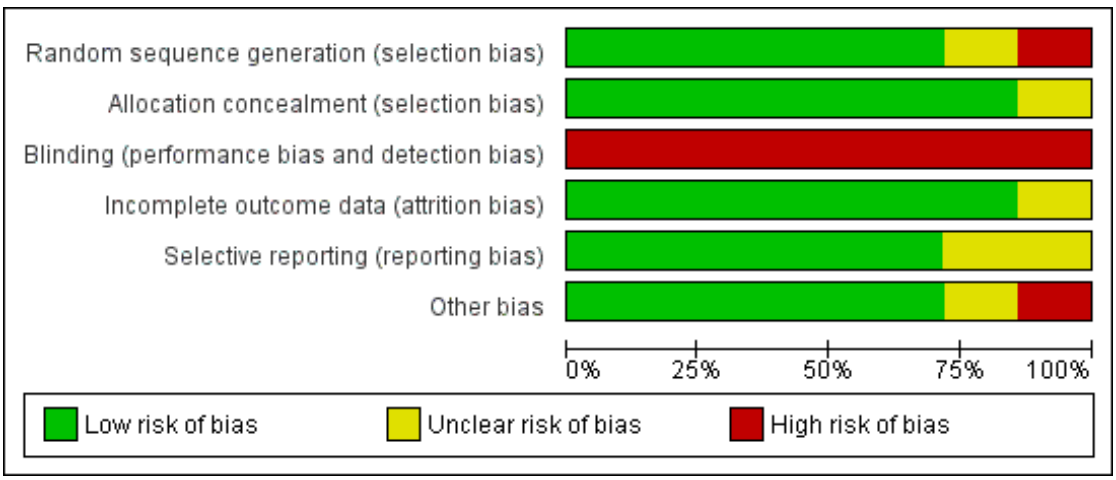
### Data extraction and management

Each review author extracted data separately to a data extraction form. We then compared the information and resolved differences by consensus. One review author (PS) entered data into Review Manager 5 (RevMan 5.3) and the other review author (JJH) cross-checked the printout against her own data extraction forms and the discrepancies were discussed and resolved. For the studies identified as an abstract, we contacted the primary study author to obtain further information.

### Assessment of risk of bias in included studies

The following headings and associated questions (based on the questions in the 'Risk of bias' table Figure 1) were evaluated independently by the two authors and entered into the 'Risk of bias' table.

**Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**





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1. Selection bias (random sequence generation and allocation concealment): for each included study, we categorised the risk of selection bias as:

i) low risk - adequate (any truly random process, e.g. random number table; computer random number generator);

ii) high risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);

iii) unclear risk - no or unclear information provided.

2. Allocation concealment: for each included study, we categorised the risk of bias regarding allocation concealment as:

i) low risk - adequate (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);

ii) high risk - inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);

iii) unclear risk - no or unclear information provided.

3. Blinding: for each included study, we categorised the methods used to blind study personnel (i.e. Clinician/Nurse administering the intervention) from knowledge of which intervention a participant received.

i) low risk - adequate for personnel (an attempt was made to conceal the intervention and control from the study personnel);

ii) high risk - inadequate (personnel aware of group assignment);

iii) unclear risk - no or unclear information provided.

4. Detection bias: for each included study, we categorised the methods used to blind outcome assessors from knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention). Blinding was assessed separately for different classes of outcomes. We categorised the methods used as:

i) low risk - adequate follow-up was performed with assessors blinded to group assignment;

ii) high risk - inadequate (assessors at follow-up were aware of group assignment);

iii) unclear risk - no or unclear information provided.

5. Attrition bias: we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We categorised the methods with respect to the risk of attrition bias as:

i) low risk - no missing data or missing data balanced across groups;

ii) high risk - numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation;

iii) unclear risk - no or unclear information provided.

6. Reporting bias: for each included study, we described how we investigated the risk of selective outcome reporting bias and what we found. We assessed the methods as:

i) low risk - adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

ii) high risk - inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

iii) unclear risk - no or unclear information provided (the study protocol was not available).

7. Other bias: for each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

i) low risk - no concerns of other bias raised;

ii) high risk - concerns raised about multiple looks at the data with the results made known to the investigators, difference in number of patients enrolled in abstract and final publications of the paper;

iii) unclear - concerns raised about potential sources of bias that could not be verified by contacting the authors.

### Measures of treatment effect

We performed statistical analyses using RevMan 5.3. We analysed categorical data using risk ratio (RR), and number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for dichotomous outcomes. We reported the 95% confidence interval (CI) on all estimates. If we had encountered any continuous outcomes we would have reported mean difference and 95% CI.

### Unit of analysis issues

There were no unit of analysis issues since we found no cluster RCTs or cross-over studies. We have reported how each study that randomised twins dealt with this potential clustering effect. For trials testing more than two arms if encountered, we intended to include only the arms relevant to our objective in the analysis.


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Where two or more arms met our inclusion criteria for either the intervention of the control we intended to combine those arms.

### Dealing with missing data

We contacted the authors of studies with missing data that could be included in the analysis. For included studies,we have noted levels of attrition. If we had encountered studies with high levels of missing data in the overall assessment of treatment effect we intended to explore the impact of this using sensitivity analysis. For all analyses carried out, we used an intention-to-treat principle i.e. we included all participants in the analysis in the group they were randomised to. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

### Assessment of heterogeneity

We first inspected each forest plot for any lack of overlap of confidence intervals as evidence of heterogeneity. We then assessed heterogeneity statistically with the $I^2$ statistical test. An $I^2$ estimate of more than 50% was considered moderate heterogeneity and more than 75% as substantial heterogeneity.

### Assessment of reporting biases

If we had found 10 or more included studies we intended to construct a funnel plot. We would have visually inspected the funnel plot for asymmetry and if detected we would have attempted to explain it.

### Data synthesis

We used the statistical package in Review Manager 5 (RevMan 5.3) provided by Cochrane. We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and trial populations and methods were judged sufficiently similar.

### Quality of evidence

The quality of evidence reflects the extent to which we are confident that the estimate of the effect is correct (Schünemann 2013). We assessed the quality of evidence for the two main comparisons at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011d). This methodological approach considers randomised controlled trials as high-quality evidence that may be 'down-rated' by limitations in any of five areas: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias (Guyatt 2011d). The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades: 1) High: We are very confident that the true effect lies close to that of the estimate of the effect; 2) Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; 3) Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; 4) Very Low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect (Schünemann 2013).

We independently assessed the quality of the evidence found for outcomes identified as critical or important for clinical decision making. Outcomes for CPAP compared with supported care were: failed treatment, bronchopulmonary dysplasia at 36 weeks' postmenstrual age (defined as supplemental oxygen at 36 weeks' gestation), bronchopulmonary dysplasia or death at 36 weeks' postmenstrual age, pulmonary air leak syndromes (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema), intraventricular haemorrhages (grades 3 and 4), and neurodevelopmental outcome (measured on a validated scale that measures cognitive, motor, behavioural function or blindness, deafness, or cerebral palsy at about 2 years of age).

For the comparison of CPAP with assisted ventilation, outcomes assessed were: mortality at 28 to 30 days and at hospital discharge, bronchopulmonary dysplasia at 36 weeks' postmenstrual age (defined as supplemental oxygen at 36 weeks' gestation), bronchopulmonary dysplasia or death at 36 weeks' postmenstrual age, pulmonary air leak syndromes (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema), intraventricular haemorrhages (grades 3 and 4), and neurodevelopmental outcome (measured on a validated scale that measures cognitive, motor, behavioural function, or blindness, deafness, or cerebral palsy at about 2 years of age).

In cases where study authors did not take measures to ensure concealment of allocation, randomised assignment, completed follow-up or blinded outcome assessment, we downgraded the quality of evidence because of design limitations (Guyatt 2011b). We evaluated consistency by similarity of point estimates, extent of overlap of confidence intervals and statistical criteria including a test for heterogeneity ($I^2$). We downgraded the quality of evidence when inconsistency across studies' results was present, large and unexplained (i.e. some studies suggest important benefit; and others no effect or harm without a clinical explanation) (Guyatt 2011a). We used the 95% confidence interval around the pooled estimation to assess for precision (Guyatt 2011e). When trials were conducted in populations other than the target population, we downgraded the quality of evidence because of indirectness (Guyatt 2011c).

We entered data (i.e. pooled estimates of the effects and corresponding 95% confidence Intervals) and explicit judgements for each of the above assessed aspects into GRADEprofiler (GRADEpro 2008), the software used to create 'Summary of findings' (SoF) tables. All judgements involved in the assessment of the


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study characteristics described above are explained in footnotes or comments in the SoF tables.

### Subgroup analysis and investigation of heterogeneity

We investigated heterogeneity by first attempting to explain it based on the trial characteristics and methods. We then performed a limited number of prespecified subgroup analyses as follows. For the primary outcomes subgroup analysis was planned to address the following hypotheses:

1. Infants born at the lowest gestational ages (e.g. < 28 weeks or with a birth weight < 1000 grams) are less likely to respond in terms of avoiding IPPV.
2. Use of CPAP at higher pressures will be more effective than administration at lower pressures.
3. Use of CPAP via the nose rather than via intubation of the pharynx, trachea or other modes will be more effective.
4. Early treatment with CPAP is as effective as assisted ventilation with or without surfactant as the initial support for extremely-low-birth-weight infants (Comparison 2 only).
5. CPAP would be more effective in studies with a high usage of antenatal steroids (e.g. more than 50%)

Of these we were not able to do subgroup analysis with regard to CPAP or the use of antenatal steroids.

### Sensitivity analysis

We planned to conduct a sensitivity analysis to explore differences in trial quality. In the first two version of this review we used the fixed-effect model. For this version we did sensitivity analysis using random-effects meta-analysis when we encountered moderate heterogeneity.

## RESULTS

### Description of studies

#### Results of the search

For this update, we screened 4963 citations (Figure 2), and of these we retrieved the full text for seven new studies. Of these, five were included and the other two were excluded. In addition, one further study in abstract form which was classified as 'waiting further assessment' was excluded (Thomson 2002).


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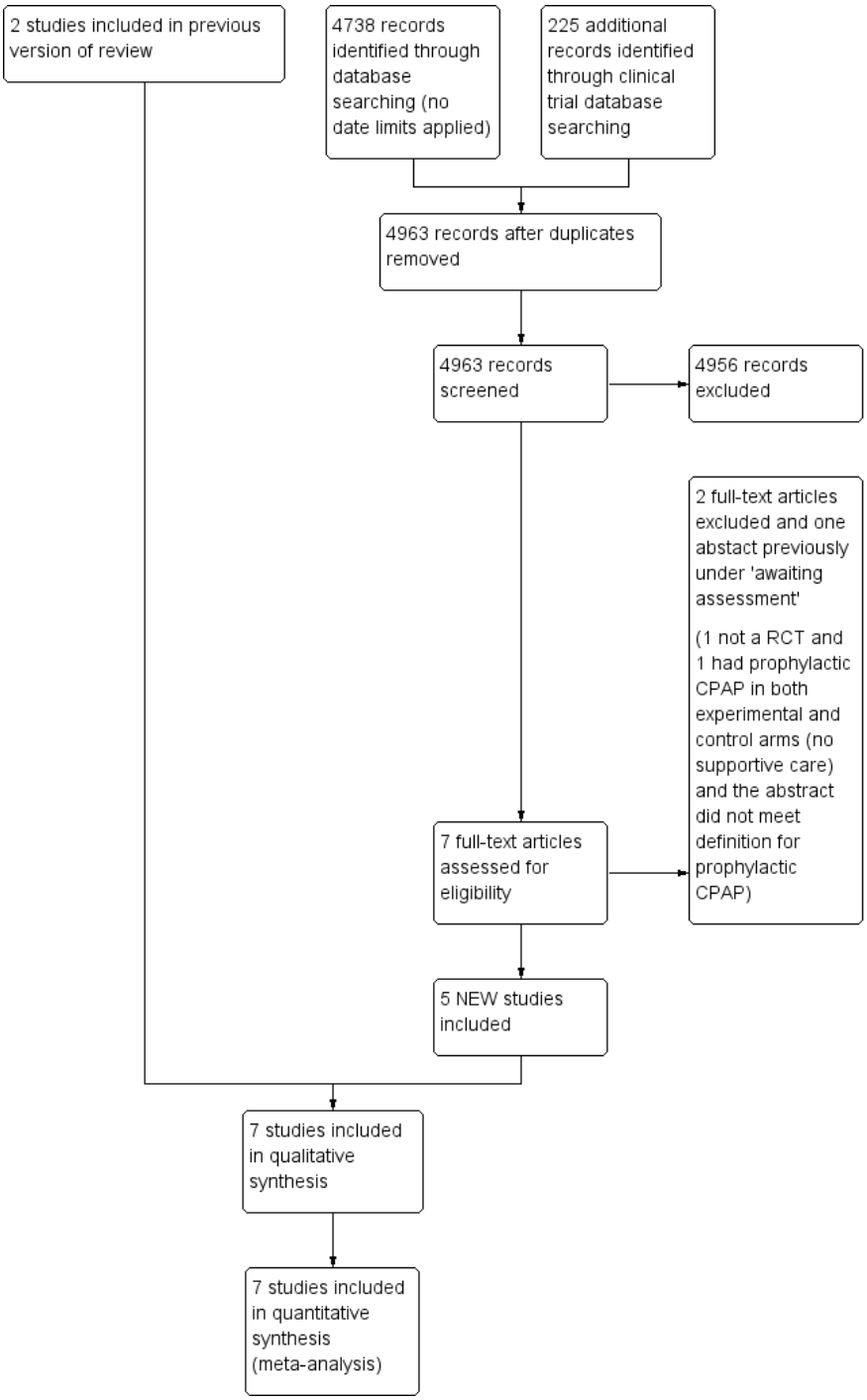
**Figure 2. Study flow diagram: review update**





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### Included studies

The previous update included two studies (Han 1987; Sandri 2004). For this update seven more studies were evaluated (Dunn 2011; Finer 2010; Gonçalves-Ferri 2014; Morley 2008; Rojas 2009; Tapia 2012; Zaharie 2008). We included five new studies bringing it to a total of seven included studies recruiting a total of 2342 infants included in the final analysis (Dunn 2011; Finer 2010; Gonçalves-Ferri 2014; Han 1987; Morley 2008; Sandri 2004; Tapia 2012). Full details of the seven included studies are given in the Table of Characteristics of included studies. All studies were parallel-arm randomised controlled trials. One study had three arms of which two were relevant to our study (Dunn 2011). We excluded the arm randomising infants to the INSURE technique. Finer 2010 used a two-by-two factorial design to study two interventions (prophylactic CPAP versus control and oxygen saturation targeting 85% to 89% versus 91% to 95%).

### Participants

Han 1987 included 82 spontaneously breathing infants who were less than 33 weeks' gestation, within two hours of life and without major congenital malformation. No mother received antenatal corticosteroids and surfactant therapy was not available. The mean gestational ages (GAs) were 29.4 and 30 weeks and mean birth weights 1290 and 1400 grams for intervention and control groups respectively.

In the Sandri 2004 study 230 infants of 28 to 31 weeks' gestation were randomised in the delivery room to receive the intervention or control within 30 minutes of life. Prenatal corticosteroids steroids were given to the mothers of 83.3% of the infants in the CPAP group and 82.4% of the infants in the control group. Surfactant was given to 22.6% of the infants in the CPAP group and 21.7% in the control group. The mean GAs were 30 and 29.9 weeks and mean birth weights 1370 and 1339 grams for intervention and control groups respectively. For twin deliveries only the first twin was included.

The Morley 2008 study included 616 Infants of a gestational age ranging from 25 weeks to 28 weeks 6 days with no known condition that might adversely affect breathing after birth apart from prematurity and who were judged to require respiratory support at five minutes of age. Prenatal corticosteroids were given to the mothers of 94% of infants in both groups. Surfactant was given to 38% of infants in the CPAP group and 77% in the control group. The mean gestational age and birth weights of each group were 26.9 and 26.87 weeks and 964 grams and 952 grams for intervention and control groups respectively.

In the Finer 2010 study 1361 infants of a gestational age ranging from 24 weeks to 27 weeks 6 days with no known condition that might adversely affect breathing after birth apart from prematurity were randomised prior to birth. Multiple births were all assigned to the same group. Prenatal corticosteroids were given to 96.8% in the CPAP group of which 73.6% received a full course; and in the ventilated group 95.6% received steroids of which 69.8% received a full course. Surfactant was given to 67.1% of the CPAP group and 98.9% of the ventilated group In the delivery room or NICU. The mean GAs for the CPAP and control groups were 26.2 and 26.2 weeks and mean birth weights 834.6 and 825.5 grams.

In the Dunn 2011 study 656 infants between 26 weeks and 29 weeks 6 days were randomised at birth to three groups, two of which were included in our study (n = 432). Twins or other multiples were randomised separately. Prenatal corticosteroids were given to 98.7% of the CPAP group and 98.6% of the intubated group. Surfactant was given to 14.8% of the CPAP group and 98.6% of the intubated group. The mean GAs for both groups were 26.9 weeks and mean birth weights were 964 grams and 952 grams for intervention and control groups respectively.

In the Tapia 2012 study 256 infants with birth weights of greater than or equal to 800 grams and less than or equal to 1500 grams without malformations and who were spontaneously breathing at five minutes of life were included. Twins were included (21.4% and 23.2% of the CPAP group and control group respectively) but it is not stated how twins were randomised. Antenatal steroid was used in 90.8% of the CPAP group and 88.0% of the control group.and surfactant in 27.5% and 46.4% of intervention group and control group respectively. For both the CPAP and control groups the mean GAs were 29.8 weeks and 29.5 weeks and mean birth weights 1196 and 1197 grams respectively.

Gonçalves-Ferri 2014 included 197 infants who were premature newborns with a birth weight of 1000 to 1500 grams and without major malformations who were spontaneously breathing at 15 minutes of life. Antenatal steroids was administered to the mothers of 66 babies in the CPAP group and 63 babies in the control group. For the CPAP and control groups the mean birth weights were 1262 and 1286 grams respectively and mean GAs were 31.2 weeks for both groups. For twin pregnancies only the first twin was included.

### Intervention

In Han 1987 the experimental group received nasal CPAP via the nasopharyngeal route and the control group received supportive care. The optimal level of CPAP was determined by measuring pressure in the lower oesophagus (Tanswell 1980). The control group received oxygen via head box and CPAP was initiated according to criteria in the protocol. Thirty-three per cent of the control infants received CPAP and 11 of these 13 infants received it within the first six hours of life.


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In Sandri 2004, six centimetres of nasal CPAP was used delivered by a CPAP driver through nasal prongs. The control group received head box oxygen; if this failed according to predetermined criteria CPAP was started. In the control group, 66 infants (57.4%) received CPAP at a median age of 108.5 minutes.

In Morley 2008, 8 cm$H_2O$ with short single or double prong nasal CPAP was initially used and after admission to the nursery a double prong was used and the CPAP pressure could be altered as required. Intubation and mechanical ventilation was initiated only if strict criteria were met. The control group received intubation and mechanical ventilation. Surfactant was not mandatory but could be administered to either treatment group after intubation.
In Finer 2010 infants in the CPAP group were resuscitated according to the neonatal resuscitation programme guideline. CPAP was delivered by a T-piece resuscitator, ventilator or an equivalent device at 5 cm$H_2O$. If they required intubation for the purpose of resuscitation, surfactant was administered. They subsequently received nasal CPAP in the NICU via a ventilator, purpose-built flow driver or bubble CPAP circuit. Intubation was only performed after arrival in the NICU if the infant met strict predetermined criteria and surfactant was administered if the infant was under 48 hours of life. Control infants received intubation and surfactant in the delivery room and could be extubated within 24 hours if they met predetermined criteria. Delivery room CPAP was received by 81.1% and 22.4% of the CPAP and control groups respectively.
In Dunn 2011 nasal CPAP was administered in the delivery room within 15 minutes of life initially at a pressure of 5 cm$H_2O$, which could be increased to a maximum of 7 cm $H_2O$. Short, binasal prongs were used as the interface. All infants received bubble CPAP generated by continuous gas flow delivered through a heated, humidified circuit with the end submerged to an appropriate depth in a water-filled bottle. The control group were intubated at 5 to 15 minutes of life and administered surfactant. Infants remained intubated for a minimum of six hours of life. Delivery room CPAP was received by 91% and 5.3% of the experimental and control groups, respectively. A third group, not included in our study, received intubation and surfactant at 5 to 15 minutes of life followed by extubation to CPAP.
In Tapia 2012 study Infants were given CPAP (as soon as possible after allocation) using a bubble CPAP system (Fisher & Paykel Healthcare) with a distending pressure of 5 cm $H_2O$. The short binasal prongs included with the CPAP system were used. Prior to insertion of the nasal prongs CPAP was maintained at 5 cm$H_2O$ through a mask connected to a T-piece resuscitator ensuring that the infants in this group were maintained on CPAP from the time of enrolment. If the infant reached predetermined criteria an endotracheal tube was inserted and surfactant was administered followed by extubation to CPAP according to the INSURE protocol (Stevens 2008). CPAP could be increased to 7 cm$H_2O$. The control group received oxygen as required by a head box or low flow oxygen canula and were intubated and received mechanical ventilation and surfactant according to predetermined criteria.
For the infants in Gonçalves-Ferri 2014 who were randomised to CPAP, positive pressure was applied using a Neopuff TM manual ventilator with PEEP at 5 cm$H_2O$ 0 and 100% oxygen in the delivery room. The control group received routine treatment which included oxygen delivered by methods described in the AAP and AHA guideline (Kattwinkel 2010). After transfer to the Neonatal Intensive Care Unit, infants were stabilised and ventilation parameters followed institutional protocols. The CPAP group was maintained with positive pressure for at least 48 hours.
For Comparison 1 (Prophylactic CPAP versus supportive care), we included Han 1987, Sandri 2004, Tapia 2012 and Gonçalves-Ferri 2014; and for Comparison 2 (Prophylactic CPAP versus assisted ventilation) we included Dunn 2011, Finer 2010 and Morley 2008.

### Outcomes

A number of outcomes were not defined by the authors in the first published paper but have been clarified by contact with Dr Han (see Characteristics of included studies) (Han 1987). The outcomes defined in Sandri 2004 included neonatal death, IVH of greater than grade 2, PVL, ROP greater than grade 2, necrotising enterocolitis (NEC), sepsis, BPD (oxygen at 36 weeks postmenstrual age), air leaks and patent ductus arteriosus (PDA).
The primary outcomes defined by both Morley 2008 and Finer 2010 were death and BPD. Morley 2008's secondary outcomes were the incidence of intubation, reasons for intubation, the need for oxygen treatment at 28 days, the fraction of inspired oxygen ($FiO_2$) at 36 weeks' gestational age, the incidence of air leaks and intracranial haemorrhages, the duration of ventilation and CPAP, the number of days in the hospital, the number of days to regain birth weight, methylxanthine treatment, treatment with postnatal corticosteroids and the dose of surfactant.
Secondary outcomes defined by Finer 2010 included pneumothorax (in the first 14 days), IVH (grades 3 or 4), and the need for chest compressions or epinephrine during resuscitation, NEC, postnatal corticosteroid therapy for BPD, and severe ROP among survivors
The primary outcomes defined by Dunn 2011 included death or moderate to severe BPD at 36 weeks. Secondary outcomes included the number of infants who received surfactant, number of surfactant doses, use of postnatal steroids, growth, days on assisted ventilation, days on nasal CPAP, days on supplemental oxygen, pneumothorax, pulmonary haemorrhage, PDA, NEC, sepsis, IVH, PVL and ROP.
In the Tapia 2012 study, the primary outcome was any requirement for mechanical ventilation and the secondary outcomes included


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death, use of surfactant, pneumothorax, IVH, PDA, late-onset sepsis, ROP, BPD, days of oxygen therapy, days of mechanical ventilation, and length of hospital stay.

The primary outcome for Gonçalves-Ferri 2014 was use of mechanical ventilation or surfactant, or both, during the first five days of life. Further details of the management of the control group were supplied by the authors. According to the study protocol infants in the control group who failed supportive therapy should be administered CPAP prior to the use of mechanical ventilation. We therefore used the number of infants who received CPAP for our primary outcome of failed treatment. Failed CPAP for the intervention group consisted of the number of infants who received assisted ventilation. Secondary outcome was morbidity and mortality during hospital stay. Data on mortality and BPD was received from the authors.

Adverse effects reported included subglottic stenosis (Han 1987); and nasal injury (Tapia 2012).

Further details of the included trials can be found in the table of Characteristics of included studies.

#### Other completed or ongoing studies

Our search did not reveal any additional on-going studies.

### Excluded studies

In previous updates, we excluded two studies (Drew 1982; Tooley 2003). For this update, we excluded three studies (Rojas 2009; Thomson 2002; Zaharie 2008), Of these, we excluded Rojas 2009 because the infants were randomly assigned to either CPAP alone or CPAP with surfactant given during a brief period of mechanical ventilation. There was no comparison with supportive care. Zaharie 2008 was not an RCT. One further study from the United Kingdom was a multi-centre RCT with four arms (n = 237) (Thomson 2002). The authors state that in the two groups of infants randomised to prophylactic CPAP about 76% (Group 1) and 79% (Group 2) of the participants were on prophylactic CPAP by six hours of life. Therefore it is highly unlikely that this study meets our inclusion criteria of prophylactic CPAP starting within 15 minutes of life. In addition this study was only published as an abstract with insufficient data to include in the analysis. Of note, the findings of this study were in line with our conclusion that CPAP reduces the need for mechanical ventilation. Further details of the excluded studies are available in the table of Characteristics of excluded studies.

### Risk of bias in included studies

Details are given in the Characteristics of included studies and in Figure 3. In the Han 1987 trial, randomisation was concealed but treatment was not blinded. Five infants (10%) were excluded after randomisation (two treatment, three control). Three of these were excluded for treatment violations; therefore this study was not strictly analysed according to an intention-to-treat principle. There was blinding of the assessment of radiological outcomes for BPD. The trial stopped early because of concern raised during the second planned interim analysis; after entry of 30 infants, the outcomes in the treatment group were possibly worse. In the Sandri 2004 trial randomisation was concealed by use of a central telephone service and stratified by weeks of gestational age in blocks of six but not by centre. The treatment was not blinded and it was not stated whether there was blinding of any of the outcomes. Follow-up was complete. In the Morley 2008 study randomisation was stratified according to centre and gestational age by use of a random number table and block randomisation with variable block sizes and was concealed by sequentially numbered, sealed, opaque envelopes. Finer 2010 used specially prepared double-sealed envelopes opened just prior to delivery and this was stratified by centre and gestational age group. In the Dunn 2011 study, randomisation was stratified according to centre and gestational age and this was done by an independent statistician using a random number table and block randomisation with variable block sizes. Infants were randomly allocated to the treatment arms by drawing a card contained within a sealed opaque envelope. In Tapia 2012's study a computerized randomisation system was used. The infants were stratified by birth weight (800 to 999 grams and 1000 to 1500 grams) and by centre. Allocation was obscured in sealed opaque envelopes. Gonçalves-Ferri 2014 did not specify the method of generation of the random sequence; however allocation was concealed by opaque sealed envelopes stratified into two weight groups and by centre and block randomisation of four.


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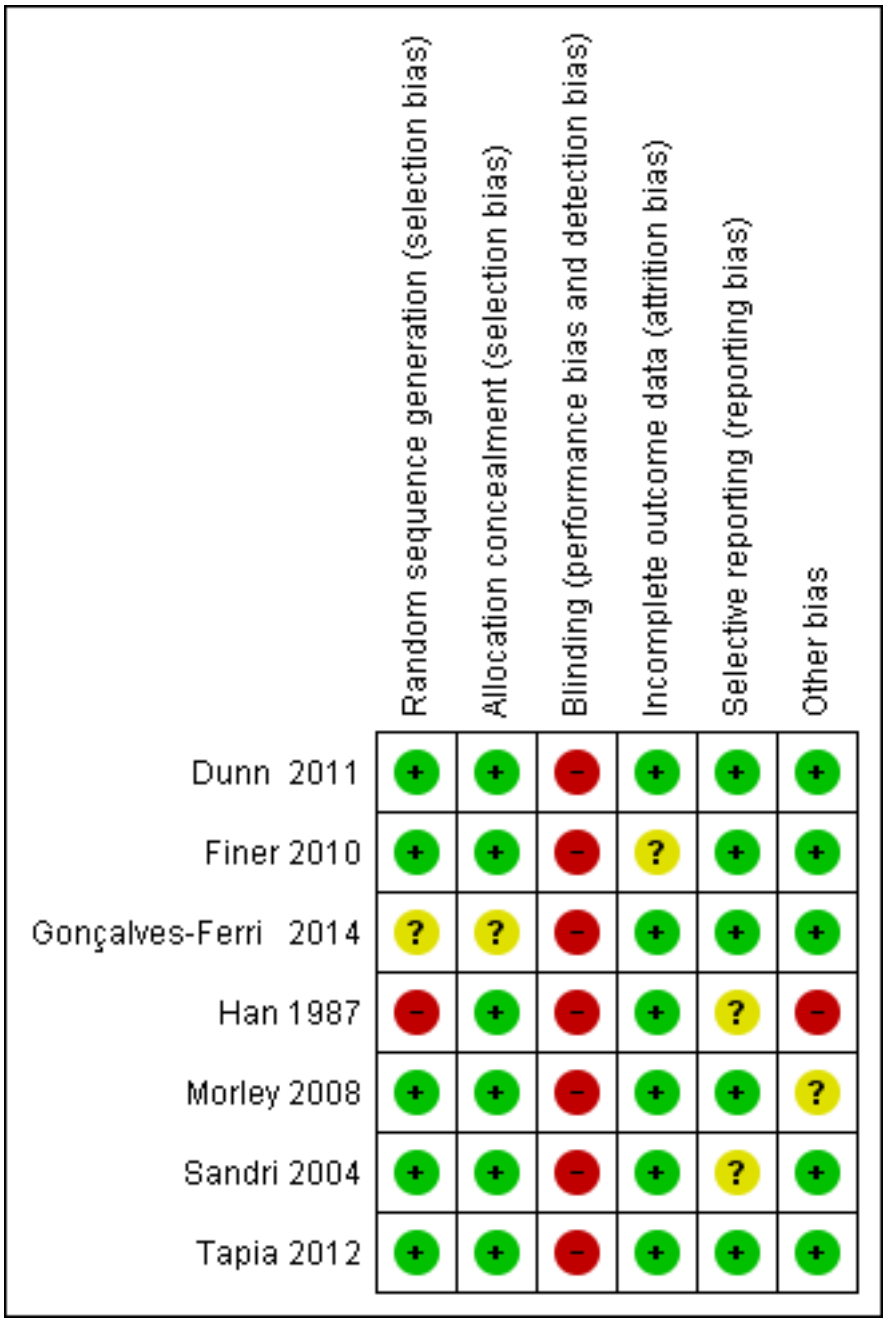
**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**





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None of the studies used blinding of the intervention to parent, caregivers, study personnel or outcome assessors except Han 1987, who used blinding of assessors for a radiological diagnosis of BPD.

## Effects of interventions

See: **Summary of findings for the main comparison** Prophylactic CPAP compared to supportive care for preventing morbidity and mortality in very preterm infants; **Summary of findings 2** Prophylactic CPAP compared to assisted ventilation for preventing morbidity and mortality in very preterm infants

We included seven studies involving a total of 3129 infants (Dunn 2011; Finer 2010; Gonçalves-Ferri 2014; Han 1987; Morley 2008; Sandri 2004; Tapia 2012). Four trials on 765 infants were included in the first comparison (CPAP versus supportive care) (Gonçalves-Ferri 2014; Han 1987; Sandri 2004; Tapia 2012); and three studies on 2364 infants were included in the second comparison (CPAP versus mechanical ventilation) (Dunn 2011; Finer 2010; Morley 2008).

### Prophylactic CPAP versus supportive care (comparison 1):

#### Failed treatment, use of assisted ventilation (outcome 1.1)

Four trials (765 participants) reported on this outcome ( Gonçalves-Ferri 2014; Han 1987; Sandri 2004; Tapia 2012) (Analysis 1.1). For three studies failed treatment was defined as the use of assisted ventilation; and for one study it was defined as use of rescue CPAP prior to the use of mechanical ventilation, surfactant, or both (Gonçalves-Ferri 2014). In Han 1987 and Sandri 2004 there is no significant difference in the use of IPPV between CPAP and control groups. However in Tapia 2012 and Gonçalves-Ferri 2014 the CPAP group had significantly lower rates of failed treatment compared to the supportive care group. The meta-analysis of the four studies showed a reduction in failed treatment (typical RR 0.66, 95% CI 0.45 to 0.98; typical RD −0.16, 95% CI −0.34 to 0.02; 4 studies, 765 infants, random effects) (Gonçalves-Ferri 2014; Han 1987; Sandri 2004; Tapia 2012). There was substantial heterogeneity using the fixed-effect model ($I^2$ = 70%); therefore the above treatment estimates are derived using the random-effects model. Subgroup analysis by birth weight did not explain this heterogeneity (typical RR 0.70, 95% CI 0.41 to 1.18; $I^2$ = 77%) for infants greater than 1000 grams (3 trials, 716 infants, random effects, test for subgroup differences $I^2$ = 0% and P = 0.66). The available data do not permit the other planned subgroup analyses. Outcome was downgraded to very low quality evidence for substantial heterogeneity, imprecision and the outcome being susceptible to the lack of blinding of the intervention and outcome assessors.

#### Bronchopulmonary dysplasia (BPD) (outcome 1.2, 1.3, 1.4)

There was no significant difference between CPAP and supportive care in the incidence of BPD at 28 days in the three studies reporting this (Gonçalves-Ferri 2014; Han 1987; Tapia 2012) (typical RR 1.02, 95% CI 0.77 to 1.36, 535 participants, $I^2$ = 38%) (Analysis 1.2). There was also no significant difference in the outcome BPD at 36 weeks (typical RR 0.79, 95% CI 0.50 to 1.24; 683 participants, 3 studies, $I^2$ = 14% (Gonçalves-Ferri 2014; Sandri 2004; Tapia 2012) (Analysis 1.4). There was no significant difference between the birth weight subgroups for BPD using either of the two BPD definitions. A subgroup analysis was possible by use of antenatal corticosteroids for the two studies that reported BPD at 28 days and it showed no significant subgroup difference in this outcome between the groups; however there was moderate heterogeneity (Analysis 1.3) (Han 1987; Tapia 2012). The outcome was downgraded to moderate quality due to imprecision.

#### Mortality (outcome 1.5)

Neonatal mortality was available for four studies (Gonçalves-Ferri 2014; Han 1987; Sandri 2004; Tapia 2012). There was no significant difference in mortality in any of the individual studies or in the overall meta-analysis, (typical RR 1.04, 95% CI 0.56 to 1.93; 765 participants, $I^2$ = 0%) (Analysis 1.5). Outcome was downgraded to moderate quality because of imprecision.

#### Death or bronchopulmonary dysplasia (outcome 1.6)

Death or bronchopulmonary dysplasia was reported only by Tapia 2012. No significant difference in rates was found between CPAP and supportive care groups (RR 0.69, 95% CI 0.40 to 1.19, one study, 256 infants) (Analysis 1.6). This outcome was downgraded to moderate-quality evidence due to imprecision.

#### Use of surfactant (outcome 1.7)

Three studies reported the use of surfactant in the two groups (Gonçalves-Ferri 2014; Sandri 2004; Tapia 2012). Only one of the individual studies showed a statistically significant decrease in the use of surfactant and the overall meta-analysis favoured the CPAP group (typical RR 0.75, 95% CI 0.58 to 0.96, 3 studies, 683 infants, $I^2$ = 50.6%) (Analysis 1.7) (Tapia 2012). We judged this to be a subjective outcome that could be influenced by lack of blinding and therefore the evidence was downgraded to low quality due to lack of blinding and imprecision. Subgroup analysis by birth weight did not explain the heterogeneity. Data were not available for the other planned subgroup analyses.


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#### Pneumothorax (outcome 1.8)

All three studies reported the rates of pneumothorax (Gonçalves-Ferri 2014; Sandri 2004; Tapia 2012). There are no significant difference in the rates between CPAP and supportive care in any study or in the meta-analysis (typical RR 0.75, 95% CI 0.35 to 1.61, 3 trials, 586 infants, $I^2$ = 0%) (Analysis 1.8). The evidence was judged to be of moderate quality due to imprecision. We judged this to be an objective outcome so did not downgrade for lack of blinding.

#### Local trauma (outcome 1.9)

Subglottic stenosis was only reported by Han 1987. There was one report out of the 82 included infants occurring in the supportive care group. No significant difference was found. Tapia 2012 reported nasal injury in 11 out of 131 infants in the CPAP group, favouring supportive care (RR 21.95, 95% CI 1.31 to 368.65; RD 0.08, 95% CI 0.03 to 0.13, NNTH 13, 95% CI 33 to 8, 256 infants) (Analysis 1.9).

#### Intraventricular haemorrhage (IVH) (outcome 1.10, 1.11)

Han 1987 and Tapia 2012 reported IVH of any grade. There was no significant difference in either study or the meta-analysis (typical RR 1.42, 95% CI 0.94 to 2.13, 2 studies, 338 infants, $I^2$ = 4%) (Analysis 1.10). Both Sandri 2004 and Tapia 2012 reported grades 3 or 4 IVH, however neither study or the meta-analysis showed any significant difference (typical RR 0.96, 95% CI 0.39 to 2.37, 2 studies, 486 infants, $I^2$ = 23%) (Analysis 1.11). Moderate-quality evidence (downgraded due to imprecision).

#### Periventricular leukomalacia (PVL) (outcome 1.12)

PVL was only reported by Sandri 2004 who found no significant difference between the CPAP and control groups (Analysis 1.12).

#### Necrotizing enterocolitis (NEC) (outcome 1.13)

There was no significant difference in each of the individual studies or overall (typical RR 0.91, 95% CI 0.55 to 1.50, 568 infants, $I^2$ = 34%) (Analysis 1.13) (Han 1987; Sandri 2004; Tapia 2012).

#### Sepsis (Outcome 1.14)

Rates of sepsis were reported in three studies (Han 1987; Sandri 2004; Tapia 2012). There are no significant differences in any of the individual studies or in the meta-analysis (typical RR 1.04, 95% CI 0.64 to 1.69, 568 infants, $I^2$ = 0%) (Analysis 1.14).

#### Retinopathy of prematurity (ROP) (outcome 1.15)

Rates of ROP grades 3 or 4 were reported in two studies (Han 1987; Sandri 2004). There are no difference in either study or in the meta-analysis (typical RR 0.67, 95% CI 0.13 to 3.32, 312 infants, $I^2$ = 0%) (Analysis 1.15).

Failure of treatment as indicated by recurrent apneas, hypoxia, hypercarbia ($PaCO_2$ > 60) and increasing $FiO_2$ requirement, the use of health care resources, and the neurodevelopmental status of the infants at follow-up were not reported in any study.

### Prophylactic CPAP versus assisted ventilation (comparison 2)

#### Bronchopulmonary dysplasia (BPD) (outcome 2.1, 2.2, 2.3)

Three studies reported this outcome (Dunn 2011; Finer 2010; Morley 2008). In the one study that reported BPD at 28 days there was also a significant reduction in the CPAP group (RR 0.81, 95% CI 0.70 to 0.94, one study, 610 infants) (Analysis 2.1) (Morley 2008). None of the included studies showed a significant reduction in BPD at 36 weeks but in the meta-analysis there was a significant reduction (typical RR 0.89, 95% CI 0.80 to 0.99, 3 studies, 2150 infants; typical RD −0.04, 95% CI −0.08 to 0.00, NNTB 25, 95% CI 13 to 100, $I^2$ = 0%, moderate-quality evidence) (Analysis 2.2, Analysis 2.3). We judged that this outcome would not be influenced by the lack of blinding of the intervention but quality would be influenced by imprecision.

#### Neonatal death (outcome 2.4, 2.5)

Neonatal mortality was reported for a total of 2358 infants in the three studies (Dunn 2011; Finer 2010; Morley 2008). There was no significant difference in mortality between the CPAP and ventilation groups (RR 0.82, 95% CI 0.66 to 1.03, 2358 infants, $I^2$ = 0%, moderate-quality evidence) (Analysis 2.4, Analysis 2.5). We judged that this outcome would not be influenced by the lack of blinding of the intervention but quality would be influenced by imprecision.

#### Death or bronchopulmonary dysplasia (outcome 2.6, 2.7)

Death or BPD was reported by Dunn 2011, Finer 2010, and Morley 2008 in 2358 infants. There was a significant reduction in the rate of death or BDP in the CPAP group (RR 0.89, 95% CI 0.81 to 0.97; RD −0.05, 95% CI −0.09 to −0.01; NNTB 20, 95% CI 11 to 100, 3 studies, 2350 infants, $I^2$ = 0%, moderate-quality evidence) (Analysis 2.6, Analysis 2.7). We judged that this outcome would not be influenced by the lack of blinding of the intervention but quality would be influenced by imprecision.


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#### Assisted ventilation (outcome 2.8)

Two studies reported the need for assisted ventilation (Dunn 2011; Morley 2008). Both studies reported a significant reduction in the need for assisted ventilation. In the meta-analysis, both studies showed a significant reduction in the CPAP group. Although the meta-analysis suggested moderate heterogeneity, in the overall meta-analysis CPAP resulted in a significant reduction in the use of assisted ventilation (RR 0.49, 95% CI 0.45 to 0.54, 2 studies, 1042 infants, $I^2$ = 71%, P = 0.06) (Analysis 2.8). The results were not substantially altered using a random-effects model for the meta-analysis. On subgroup analysis (5 vs 8 $cmH_2O$) there was a trend for a reduced need for assisted ventilation in the trial using 8 $cmH_2O$ (RR 0.46, 95% CI 0.41 to 0.52), compared with the trial using 5 $cmH_2O$ (RR 0.54, 95% CI 0.48 to 0.62, test for subgroup differences: P = 0.07, $I^2$ = 70.5%) (Morley 2008; Dunn 2011). The quality of evidence for this outcome was downgraded because the decision to provide assisted ventilation is a subjective outcome susceptible to the lack of blinding of the intervention and outcomes assessors.

#### Use of surfactant (outcome 2.9)

For two studies surfactant was mandatory in the control group (Dunn 2011; Finer 2010); and for one study, surfactant was not mandated (Morley 2008). All three studies allowed the use of surfactant in the treatment group if intubation was required (Dunn 2011; Finer 2010; Morley 2008). All three showed a significant reduction in the use of surfactant. When combined in the meta-analysis there was substantial heterogeneity between the studies (RR 0.54, 95% CI 0.40 to 0.73; RD −0.41, 95% CI −0.54 to −0.28; NNTB 2, 95% CI 1 to 6, $I^2$ = 96%, P < 0.00001, 3 studies, 2354 infants, random effects; low-quality evidence due to lack of blinding and imprecision) (Analysis 2.9).

#### Pneumothorax (outcome 2.10)

All three studies reported the rates of pneumothorax, and there was no overall significant difference (RR 1.24, 95% CI 0.91 to 1.69, 3 studies, 2357 infants, $I^2$ = 75%). There was substantial heterogeneity and this could be explained on subgroup analysis by starting CPAP pressures (5 $cmH_2O$ vs 8 $cmH_2O$). In the analysis of the studies receiving 5 $cmH_2O$ (RR 0.96, 95% CI 0.67 to 1.37, 2 studies, 1747 infants, $I^2$ = 0%) (Dunn 2011; Finer 2010) and in the study using 8 $cmH_2O$ (Morley 2008), there was a significant increase in pneumothorax in the CPAP group (RR 3.07, 95% CI 1.47 to 6.40, one study, 610 infants), test for subgroup differences P = 0.005, $I^2$ = 87.2%. This outcome was judged to have moderate-quality evidence due to the width of the confidence interval.

#### Intraventricular haemorrhage (IVH) (outcome 2.11, 2.12)

One study reported IVH of any grade, and it did not show any difference in the incidence of IVH (RR 0.95, 95% CI 0.66 to 1.36) (Analysis 2.11) (Dunn 2011). All three studies reported the incidence of grade 3 or 4 IVH. There was no significant difference in severe grades (3 or 4), (typical RR 1.09, 95% CI 0.86 to 1.39, 3 studies, 2301 infants, $I^2$ = 52%) (Analysis 2.12). We judged this to be moderate-quality evidence due to imprecision.

#### Periventricular leukomalacia (PVL) (outcome 2.13)

PVL was reported by both Dunn 2011 and Morley 2008. There was no significant difference between the CPAP and assisted ventilation group (typical RR 0.83, 95% CI 0.39 to 1.79; 2 studies; 1006 infants, $I^2$ = 0%) (Analysis 2.13).

#### Necrotizing enterocolitis (NEC) (outcome 2.14)

There was no significant difference in the incidence of NEC in the three studies (typical RR 1.19, 95% CI 0.92 to 1.55, 3 studies, 2313 infants, $I^2$ = 0%) (Analysis 2.14).

#### Sepsis (Outcome 2.15)

Rates of sepsis were reported by Dunn 2011. There was no significant difference in the rate between the CPAP and control groups (RR 0.59, 95% CI 0.33 to 1.04, 425 infants) (Analysis 2.15).

#### Retinopathy of prematurity grade 3 or 4 (outcome 2.16)

Rates of ROP grades 3 or 4 were reported by both Dunn 2011 and Finer 2010. There was no significant difference in the rates between the CPAP and assisted ventilation group in either study or in the meta-analysis (typical RR 1.03, 95% CI 0.77 to 1.39, 2 studies, 1359 infants, $I^2$ = 39%) (Analysis 2.16).

#### Local trauma

None of the studies reported this outcome.

#### Use of healthcare resources and costs

Use of healthcare resources and costs were not addressed in any of the included studies.

#### Neurodevelopmental outcomes

Long-term neurodevelopmental outcomes were not reported in any of the included studies.


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## ADDITIONAL SUMMARY OF FINDINGS [Explanation]

**Prophylactic CPAP compared to assisted ventilation for preventing morbidity and mortality in very preterm infants**

**Patient or population:** patients with preventing morbidity and mortality in very preterm infants
**Settings:** NICUs in high income countries
**Intervention:** Prophylactic CPAP
**Comparison:** assisted ventilation

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Assisted ventilation | Prophylactic CPAP | | | | |
| **Bronchopulmonary dysplasia at 36 weeks** Oxygen dependency at 36 weeks post-menstrual age | **Study population** | | **RR 0.89** (0.8 to 0.99) | 2150 (3 studies) | ⊕⊕⊕◯ **moderate**[2] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding |
| | **381 per 1000** | **339 per 1000** (304 to 377) | | | | |
| | **Moderate** | | | | | |
| | **374 per 1000** | **333 per 1000** (299 to 370) | | | | |
| **Neonatal Death** Mortality at any time | **Study population** | | **RR 0.82** (0.66 to 1.03) | 2358 (3 studies) | ⊕⊕⊕◯ **moderate**[2] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding |
| | **126 per 1000** | **103 per 1000** (83 to 130) | | | | |
| | **Moderate** | | | | | |
| | **72 per 1000** | **59 per 1000** (48 to 74) | | | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| **Death or bronchopulmonary dysplasia**<br>Death or oxygen dependency at 36 weeks' post-menstrual age | **Study population** | | **RR 0.89**<br>(0.81 to 0.97) | 2358<br>(3 studies) | ⊕⊕⊕○<br>**moderate**[2] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding |
| | **470 per 1000** | **418 per 1000**<br>(380 to 455) | | | | |
| | **Moderate** | | | | | |
| | **389 per 1000** | **346 per 1000**<br>(315 to 377) | | | | |
| **Assisted ventilation**<br>Need for mechanical ventilation[3] | **Study population** | | **RR 0.5**<br>(0.42 to 0.59) | 1042<br>(2 studies) | ⊕⊕⊕○<br>**moderate**[1] | Outcome subjective and may be susceptible to lack of blinding although in one of the two studies assisted ventilation was mandatory in the control group |
| | **982 per 1000** | **491 per 1000**<br>(413 to 580) | | | | |
| | **Moderate** | | | | | |
| | **979 per 1000** | **490 per 1000**<br>(411 to 578) | | | | |
| **Pneumothorax**<br>Any pneumothorax or air leak | **Study population** | | **RR 1.42**<br>(0.68 to 2.98) | 2357<br>(3 studies) | ⊕⊕⊕○<br>**moderate**[2] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding<br>Considerable heterogeneity explained by subgroup differences |
| | **58 per 1000** | **82 per 1000**<br>(39 to 171) | | | | |
| | **Moderate** | | | | | |
| | **48 per 1000** | **68 per 1000**<br>(33 to 143) | | | | |
| **IVH grade 3 or 4** | **Study population** | | **RR 0.98**<br>(0.64 to 1.5) | 2301<br>(3 studies) | ⊕⊕⊕○<br>**moderate**[2] | Not downgraded for lack of blinding as outcome is objective and unlikely to be susceptible to lack of blinding<br>Moderate heterogeneity - not downgraded |

| | | | | |
|---|---|---|---|---|
| | **99 per 1000** | **97 per 1000** (63 to 148) | | |
| | **Moderate** | | | |
| | **92 per 1000** | **90 per 1000** (59 to 138) | | |
| **Neurodevelop-mental outcomes** - not reported | No study reported this outcome | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) taken from the pooled risk differences of the included studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Downgraded one level for serious study limitations due to lack of blinding of intervention or outcome assessors
[2] Downgraded one level for serious imprecision because the 95% confidence interval includes appreciable benefit and harm/ appreciable harm
[3] Control group intervention was assisted ventilation in 1 study


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# DISCUSSION

## Summary of main results

This update presents new information about the effects of prophylactic CPAP over previous versions of this review. We have included five new trials and overall the results show some benefits of CPAP without any definite harms except possibly when CPAP is applied at higher pressures.

**Comparison 1.** There was a reduction in the incidence of failed treatment in the CPAP compared with supportive care group. Similarly there is no overall reduction in the use of surfactant except in a small subgroup of infants below 1000 grams, but this should be treated with caution. There is no difference in BPD at 28 days or 36 weeks postmenstrual age.

**Comparison 2**. For both outcomes, BPD and the combined outcome of death or BPD, there was a small but statistically significant and clinically important reduction in babies treated with CPAP.

Prophylactic CPAP also reduced the need for assisted ventilation by almost half, and substantially reduced the use of surfactant.

Overall there was no increase in the incidence of pneumothorax except in the small subgroup using CPAP applied at 8 cm of water. Although this finding is biologically plausible this should be treated with caution.

There is no difference in IVH, NEC, ROP or PVL. There was a non-significant trend to a reduction of sepsis in the one study which reported this outcome.

There was very little information on the effect of the interventions on local trauma such as nasal trauma, endotracheal trauma or subglottic stenosis.

## Overall completeness and applicability of evidence

Although we had insufficient studies to construct a funnel plot we have no reason to believe that we have missed any studies. The extensive search done by the Neonatal Review Group and consultation with experts in the field did not reveal any other studies. The Thomson 2002 multicentre study could not be included in our analysis because it has not been published in full. Data from that trial might affect our final conclusions about the effect of CPAP compared with supportive care.

We are more confident about the overall completeness of the evidence for Comparison 2, CPAP versus assisted ventilation. The main clinically important outcomes were reported in all the included trials, but there was no evidence from randomised controlled trials on the cost effectiveness of prophylactic CPAP.

Cost data are needed because CPAP is a simple and inexpensive form of treatment to implement and hence has implications for use in low- and middle-income countries (LMIC). Observational studies from LMIC show that there is a high incidence of RDS in very low birth weight infants, despite the frequent use of antenatal steroids (Fehlmann 2010; Fidanovski 2005). RDS also remains one of the most common causes of neonatal death in LMIC (Ravikumara 1996). Kamath 2011 stated that interventions such as oxygen and CPAP would have the greatest impact on decreasing RDS-specific mortality rates around the world. Equipment for bubble-CPAP cost 15% of the cost of the cheapest mechanical ventilator. In models of neonatal care for resource-limited countries, bubble-CPAP may be the first type of ventilatory support that is recommended. Its low cost and safety when administered makes it ideal for this purpose (Koyamaibole 2005). Vidyasagar 2011 suggested that in developing countries, CPAP may be used as a primary mode of management of RDS. He also stated that the cost of surfactant therapy may exceed the per capita GNP in some countries. Our study shows that prophylactic CPAP substantially reduces the use of surfactant and therefore would have great impact in the management of RDS in LMIC. Our study included two trials from LMIC countries (Gonçalves-Ferri 2014; Tapia 2012). Both compared CPAP to supportive care and both these studies showed a reduction in failed treatment in the CPAP group. A limitation to this review is that there is no long-term follow-up data for either comparison.

## Quality of the evidence

The trials were generally of low risk of selection bias but due to the nature of the included interventions all studies lacked blinding of the intervention. We judged that lack of blinding might influence the subjective outcomes (failed treatment, use of surfactant and assisted ventilation) but would be unlikely to affect outcomes such as BPD, neonatal mortality and the combined outcome of BPD and neonatal death, all of which have well-recognised objective definitions. After applying the GRADE criteria, all primary outcomes for both comparisons were judged moderate quality except 'failed treatment', which we judged to be very low quality evidence. Downgrading was because of imprecision. The other primary outcome was downgraded to very low quality because of lack of blinding, imprecision and unexplained heterogeneity.

There were protocol-driven definitions for failed CPAP in comparison 1 and use of assisted ventilation in comparison 2 in all studies. With these strictly controlled definitions it could be argued that the lack of blinding is less important. Reported data were generally complete and we did not find evidence of reporting biases but the study protocols were not available for some studies.

## Potential biases in the review process

The overall consistency of the results was generally high. However we encountered moderate heterogeneity in our primary outcome (failed treatment) and moderate heterogeneity for the outcome


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BPD at 28 days, both for the comparison CPAP versus supportive care.

There were too few trials in the subgroup analysis of use of antenatal steroids to draw a meaningful conclusion. However since the trials were spread out over more than two decades, this and a number of other clinical differences could explain this heterogeneity.

There was overall very good consistency in the outcomes for comparison 2 with substantial heterogeneity seen only in the use of surfactant. This is probably due to differences in the study protocols but clinical differences in the maturity of infants could also possibly explain this. Dunn 2011 included more mature infants.

The rest of the outcomes showed minimal heterogeneity. There was a lack of reporting of local trauma such as subglottic stenosis and nasal injury. Subglottic stenosis was only reported by Han 1987; and there was one report on nasal injury and these numbers were quite small (Tapia 2012).

The protocol was first written in 1997 and since then both the research questions about the use of prophylactic CPAP and the methods used for Cochrane reviews have changed and we have therefore updated our protocol substantially. In addition due to the changes in the research questions about CPAP we have had to add a second comparison which could have resulted in the reduction in the strength of our evidence.

### Agreements and disagreements with other studies or reviews

CPAP has been shown to be beneficial for preterm infants with RDS (Ho 2015); and also at extubation from mechanical ventilation (Davis 2003). This review on prophylactic CPAP strengthens the body of evidence that CPAP is beneficial in the management of the preterm infant.

## AUTHORS' CONCLUSIONS

### Implications for practice

1. CPAP compared to supportive care: in settings where the treatment choice is between CPAP and supportive care this review provides evidence that CPAP is superior to supportive care.

2. CPAP compared to assisted ventilation: there is moderate evidence that CPAP applied prophylactically within the first 15 minutes of life reduces the incidence of BPD and the combined outcome of death and BPD as well as the need for assisted ventilation. There is also moderate evidence that surfactant use is reduced.

### Implications for research

1. There is an urgent need to evaluate the cost and effectiveness of prophylactic CPAP in both low- and middle-income settings where surfactant therapy is limited. This should be compared with current methods of management available in these settings such as low flow nasal oxygen, head box or other forms of delivery of oxygen therapy that do not generate a positive pressure. Other supportive care such as warmth and nutrition should be available to both comparison groups. Trials need to be stratified for weight or gestational age to determine if differences in effectiveness occur in lighter, less mature infants. It would also be important to follow up infants into childhood where possible.

2. In high-income countries further trials to determine the best definition of CPAP failure and to evaluate alternative methods of surfactant delivery to babies managed on CPAP are required.

## ACKNOWLEDGEMENTS

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Tanswell AK, Clubb RA, Smith BT, Boston RW. Individualised continuous distending pressure applied within 6 hours of delivery in infants with respiratory distress syndrome. *Archives of Disease in Childhood* 1980;**55**(1): 33–9.

**Vidyasagar 2011**
Vidyasagar D, Velaphi S, Bhat VB. Surfactant Replacement Therapy in Developing Countries. *Neonatology* 2011;**99**(4): 355–66. [DOI: 10.1159/000326628]

**Wilkinson 2011**
Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database of Systematic Reviews* 2011, Issue 5. [DOI: 10.1002/14651858.CD006405.pub2; PUBMED: 21563154]

## References to other published versions of this review

**Subramaniam 1998**
Subramaniam P, Henderson-Smart DJ, Davis PG. Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database of Systematic Reviews* 1998, Issue 4. [DOI: 10.1002/14651858.CD001243]

**Subramaniam 2002**
Subramaniam P, Henderson-Smart DJ, Davis PG. Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database of Systematic Reviews* 2002, Issue 2. [DOI: 10.1002/14651858.CD001243.pub2]

**Subramaniam 2005**
Subramaniam P, Henderson-Smart DJ, Davis PG. Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD001243.pub2]

* *Indicates the major publication for the study*


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# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by year of study]*

**Han 1987**

| | |
|---|---|
| Methods | Randomised controlled trial |
| Participants | Characteristics: 87 infants were eligible. Preterm infants (n = 82) of 32 weeks' gestation or less and stratified by sex. Excluded were 5 infants for whom there was insufficient time to obtain parental consent before birth, major congenital abnormalities and primary apnoea at birth necessitating immediate intubation and IPPV |
| Interventions | Experimental: nasopharyngeal CPAP of 6 $cmH_2O$ pressure applied at birth. Infants who failed to improve ($PaO_2$ < 50 mmHg in optimal CPAP (see notes) and $FiO_2$ > 0.8, apneas) were managed with endotracheal (ET) CPAP and then IPPV as indicated by $PaO_2$ < 50 mmHg in $FiO_2$ > 0.9, or pH < 7.2 mainly due to $PaCO_2$ > 60 mmHg, apnoea (severity not defined) not controlled by ETCPAP<br>Control: oxygen in a head box. Nasal CPAP given when $PaO_2$ < 50 mmHg in $FiO_2$ > 0.5, or apnoea (given to 33%). Subsequent management similar to treatment group. Both groups of infants received an initial $FiO_2$ ranging from 0.3 to 0.6 |
| Outcomes | Reported on 82 infants. Failed treatment included use of IPPV and other treatment, BPD at 28 days (oxygen therapy + abnormal chest X-ray - blindly assessed), neonatal death, pulmonary air leaks (no breakdown by pneumothorax vs other available), PDA, any IVH (breakdown by grade not available), subglottic stenosis, neonatal sepsis (blood culture positive), NEC (Bell stage 2 or more), RLF (ROP grade 3 or 4) |
| Notes | Additional information provided by the author in July 2002 on randomisation, timing of deaths, definitions of outcomes - sepsis, BPD, RLF, air leaks and diagnosis of IVH.<br>Optimal CPAP was measured according to the method described by Tanswell 1980 in which a lower oesophageal pressure is used to demonstrate opening of small airways.<br>No mother received antenatal corticosteroids and postnatal surfactant therapy was not available.<br>280 subjects planned, sequential descriptive analysis (stopped early because of possible worse outcomes in treatment group)<br>Source of funding not stated. |

*Risk of bias* *Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | "This stratification ensured distribution of boys and girls in equal numbers in the two study groups. Separate cards were prepared by a statistician for both sexes, for both study groups. Each card was placed in an envelope and provided the patient's number in the study and his or her allocation to treatment or control group which had been determined from a table of random numbers. Group assignment was made by pulling the next envelope in |


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**Han 1987** (*Continued*)

| | | |
|---|---|---|
| | | sequence from the appropriate box as soon as the sex was known at birth" |
| Allocation concealment (selection bias) | Low risk | Opaque sealed envelopes were used. |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Blinding of intervention - no<br>Blinding of outcome assessment - yes for chest X-ray, no for use of IPPV |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up for 90% of participants (2 treatment and 3 control infants excluded, 2 due to congenital abnormalities and 3 for protocol violations). Therefore not strictly according to intention to treat |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. |
| Other bias | High risk | Trial stopped early because of concerns that treatment outcomes were worse in the intervention group |

**Sandri 2004**

| | |
|---|---|
| Methods | Multicentre randomised controlled trial conducted in 17 NICUs in Italy |
| Participants | Characteristics: preterm infants (n = 230) between 28 and 31.6 weeks' gestation |
| Interventions | Experimental: prophylactic nasal CPAP of 4 to 6 $cmH_2O$ applied within 30 minutes of birth (n = 115)<br>Control: received nasal CPAP when the fraction of inspired oxygen ($FiO_2$) in the hood was > 0.4 for more than 30 minutes, to maintain transcutaneous oxygen saturation ($SpO_2$) at the right hand between 93% and 96%. Nasal CPAP was given through nasal prongs using the Infant Flow Driver system (n= 115). Newborns receiving nasal CPAP at a pressure of 6 cm water pressure, requiring a $FiO_2$ > 0.4 for more than 30 minutes to maintain $SpO_2$ in the range 93% to 96% and showed radiological signs of RDS were endotracheally intubated, treated with surfactant and manually ventilated for 2 to 5 minutes. The infants were then extubated and placed on nasal CPAP if they had a good respiratory drive and maintained a satisfactory $SpO_2$ value. Criteria for mechanical ventilation (IPPV) were: persistence of a $FiO_2$ requirement of > 0.4 on nasal CPAP after surfactant administration, severe apnoea, $PaCO_2$ > 70 mmHg and pH < 7.2, or $FiO_2$ rapidly increasing above 0.8 even before 30 minutes |
| Outcomes | Failed treatment included the use of surfactant, the need for IPPV within 7 days, air leaks, death at or before 7 days, death between 8 to 28 days, neonatal death, IVH > grade 2, PVL, NEC, sepsis, chronic lung disease at 36 weeks, PDA |
| Notes | |

| ***Risk of bias*** | ***Risk of bias*** |
|---|---|


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**Sandri 2004** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated number list. |
| Allocation concealment (selection bias) | Low risk | Computer-generated numbers stratified for each week of gestational age. Randomised in blocks of 6. However the study does not appear to be stratified by centre so the risk of knowing the allocation of each 6th participant within each stratum would have been low. For twin pairs only the first twin was randomised |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Blinding of treatment - no.<br>Blinding of outcome assessments - not stated. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow up - yes. |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available. All of the study's prespecified outcomes have been reported |
| Other bias | Low risk | None detected. Souce of funding not stated. |

**Morley 2008**

| | |
|---|---|
| Methods | International multi-centre randomised controlled trial in Australia, New Zealand, USA and Europe |
| Participants | Inclusion criteria: infants (n = 616) with a gestational age at delivery between 25 weeks and 28 weeks 6 days with no known condition that might adversely affect breathing after birth apart from prematurity<br>Birth in a hospital participating in the trial.<br>Ability to breath at 5 minutes after birth but needing respiratory support because of increased respiratory effort, grunting respiration or cyanosis<br>Exclusion criteria: infants who were intubated before randomisation<br>Infants who did not require any respiratory support or oxygen |
| Interventions | Experiment Group: infants were assigned to receive nasal CPAP started at 8 $cmH_2O$ with short single or double prong and continued until met criteria for extubation according to local protocol or until met criteria for intubation (pH < 7.25, $PCO_2$ > 60 mmHg, $FiO_2$ > 0.6 or apnoea)<br>Control Group: infants were intubated and ventilated at 5 minutes of age<br>The allocated treatment was commenced within 5 minutes of life in both groups |


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**Morley 2008** (*Continued*)

| | |
|---|---|
| Outcomes | Reported on 616 neonates: the primary outcome was death or BPD (oxygen at 36 weeks)<br>Loss of participants to follow-up: 6 of 310 in intervention group and 6 of 306 in control group |
| Notes | COIN trial. Funding by NHMRC, Australia. |

***Risk of bias*** ***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | This was done by an independent statistician using a random number table and block randomisation with variable block sizes. Randomisation was stratified according to centre and gestational age, 25 to 26 and 27 to 28 weeks |
| Allocation concealment (selection bias) | Low risk | Sequentially numbered sealed opaque envelopes |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Not possible to blind staff who had to apply either CPAP or intubation. Not possible to blind outcome assessors for primary outcome |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up in 98% of cases |
| Selective reporting (reporting bias) | Low risk | Protocol not available. All of the study's prespecified outcomes have been reported |
| Other bias | Unclear risk | Study was registered retrospectively with the Australian Clinical Trials Register |

**Finer 2010**

| | |
|---|---|
| Methods | Multicentre study, randomised controlled trial conducted in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, United States<br>Multifactorial design. Infants were randomised to low- and high-oxygen saturation levels and then to the two interventions relevant to this review |
| Participants | 1316 Infants with a gestational age at delivery between 24 weeks and 27 weeks 6 days without known malformations<br>Inclusion criteria were:<br>• Birth in a centre participating in the trial<br>• A decision had been made to provide full resuscitation<br>• Written informed consent had been obtained from a parent or guardian. |


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| | |
|---|---|
| | Infants who were excluded were those who received intubation for resuscitation on the basis of standard indications specified in the Neonatal Resuscitation Program guidelines or did not meet the eligibility criteria |
| Interventions | Experimental group received nasal CPAP via a T-piece resuscitator, a neonatal ventilator or an equivalent device with a recommended pressure of 5 $cmH_2O$ in the delivery room irrespective of respiratory status. Infants were intubated if they met any of the following criteria for intubation: pH < 7.25, $PCO_2$ > 65 mmHg, $FiO_2$ > 0.5 or haemodynamic instability defined as a blood pressure that was low for gestational age, poor perfusion or both requiring volume or pressure support for 4 hours or more. The allocated treatment was commenced soon after birth (n = 663)<br>The control group were intubated within one hour of life in the delivery room and received surfactant. They could be extubated within 24 hours if they met prespecified criteria: $PaCO_2$ of less than 50 mmHg, pH > 7.30, $FiO_2$ $\geq$ 0.35, $SpO_2$ $\geq$ 88%, a mean arterial pressure of 8 $cmH_2O$ or less, a ventilator rate $\geq$ 20 breaths/minute, amplitude < twice the mean arterial pressure if on high frequency ventilation, haemodynamic stability, without clinically significant patent ductus arteriosus) (n = 653) |
| Outcomes | Reported a total of 1316 infants and the primary outcome was death or BPD at 36 weeks. Secondary outcomes: five minute Apgar score, % infants with death or neurodevelopmental impairment at 18 months, duration of mechanical ventilation during the entire NICU stay, % infants alive and off ventilation by day 7, proportion of infants receiving surfactant treatment, incidence of air leaks on admission and overall, incidence of BPD at 36 weeks using the physiologic definition of BPD, incidence of death, proportion of infants with severe IVH, proportion of infants with PVL, proportion with threshold ROP and requiring surgery for ROP, proportion requiring endotracheal intubation before 10 minutes of age, duration of oxygen supplementation, pulse oximetry values > 90%, incidence of blindness of at least one eye at 18 to 22 months' follow-up, proportion who receive postnatal steroids to prevent or treat BPD, proportion who develop necrotizing enterocolitis (NEC), proportion with cerebral palsy at 18 to 22 months' follow-up |
| Notes | SUPPORT Study. Funding from NIH grants. Some information obtained from supplementary material on publisher's web site |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | By an independent statistician |
| Allocation concealment (selection bias) | Low risk | Stratified by centre and gestational age group<br>Specially prepared double-sealed envelopes opened just before the actual delivery. Included twin pairs were assigned to the same group |


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**Finer 2010** (*Continued*)

| | | |
|---|---|---|
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Not possible to blind staff who had to apply either CPAP or intubation. Data were collected on infants during intervention phase so not possible to blind outcome assessors for primary outcome |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | All infants were accounted for and included in the analysis. There appeared to be a balance across the groups for infants who received the two ranges of oxygen targeting<br>1. Group in which the target $O_2$ sat of 85% to 89%, 54 of 336 in intervention group and 60 of 318 in control group<br>2. Group in which the target $O_2$ sat of 91% to 95%, 40 of 327 in intervention group and 54 of 335 in control group |
| Selective reporting (reporting bias) | Low risk | The study protocol is available. All of the study's pre-specified outcomes have been reported - some in the supplementary material |
| Other bias | Low risk | None detected |

**Dunn 2011**

| | |
|---|---|
| Methods | The study was a multicentre randomised controlled trial conducted at participating Vermont Oxford Network centres. Trial consisted or three interventions, two of which were relevant to this review and included in the data analysis |
| Participants | We included 432 of 656 infants. Neonates born between 26 weeks' gestation and 29 weeks 6 days' gestation were enrolled at participating Vermont Oxford Network centres. Infants could be excluded after randomisation only if found to be stillborn or to have a previously unrecognised life-threatening congenital anomaly |
| Interventions | Experimental Group: (n = 224) Infants were to be supported with nasal CPAP within 15 minutes after birth and intubated only if meeting 1 or more of the following criteria: (a) > 12 episodes of apnoea that required stimulation or more than 1 episode that required bagging in a 6-hour period; (b) $PCO_2$ > 65 mmHg on arterial or capillary blood gas; or (c) requirement for $FIO_2$ of > 0.4 to maintain oxygen saturation of 86% to 94%. Intubation was discretionary if $FIO_2$ was 0.4 to 0.6 and mandatory if $FIO_2$ > 0.6<br>Control Group: (n = 219) infants were intubated 5 to 15 minutes after birth. These infants were then given surfactant and stabilized on mechanical ventilation for a minimum of 6 hours |
| Outcomes | Reported 432 infants. The primary outcome was death or moderate to severe BPD at 36 weeks |


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**Dunn 2011** (*Continued*)

| | |
|---|---|
| | Secondary outcomes included the number of infants who received surfactant, the use of postnatal steroids, days on assisted ventilation, pneumothorax, pulmonary haemorrhage, PDA, NEC, IVH (severe), PVL, ROP |
| Notes | Source of funding not stated |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Investigators randomly allocated infants to the different treatment arms by drawing a card contained within a sealed envelope<br>Stratification and block randomisation was according to centre and according to gestational age. Block size not stated. Infants from multiple gestation pregnancies were randomly assigned as individual subjects. Infants from multiple gestations were assigned as a single infant |
| Allocation concealment (selection bias) | Low risk | A sealed envelope was used. |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Blinding of intervention - no.<br>Blinding of outcome assessment - not for use of IPPV. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up - in 99% of cases in the treatment group and 98% in the control group, (1 treatment and 4 control infants excluded due to major birth defect; no consent; and 2 were stillborn) |
| Selective reporting (reporting bias) | Low risk | Protocol available. All of the study's prespecified outcomes have been reported |
| Other bias | Low risk | None detected |

**Tapia 2012**

| | |
|---|---|
| Methods | Randomised, controlled, multicentre trial conducted in 12 tertiary neonatal intensive care units from 5 South American countries: Argentina, Chile, Paraguay, Peru, and Uruguay |
| Participants | 265 Infants preterm infants with birth weight 800 to 1500 grams who were spontaneously breathing at 5 minutes of life. Birth in a hospital participating in the trial. Ability to breath at 5 minutes after birth but needing respiratory support because of increased respiratory effort, grunting respiration or cyanosis |


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**Tapia 2012** (*Continued*)

| | |
|---|---|
| Interventions | Experiment Group:<br>131 Infants were given CPAP (as soon as possible after allocation) using a bubble CPAP system (Fisher & Paykel Healthcare) with a distending pressure of 5 $cmH_2O$. The short binasal prongs included with the CPAP system were used. Before the nasal prongs were inserted, CPAP was maintained at 5 cm $H_2O$ through a mask connected to a T-piece resuscitator, ensuring that the infants in this group were maintained on CPAP from the time of enrolment. Infants with an $FiO_2$ > 0.35 to maintain $SpO_2$ in the target range and X-ray findings compatible with RDS were intubated and given surfactant following the INSURE protocol<br>Control Group:<br>125 Infants randomised to the Oxygen/MV group who were initially managed with oxygen via low flow nasal cannula were transferred to an oxyhood. A chest X-ray was obtained within the first 2 hours of life if there was clinical evidence of respiratory distress. In infants with RDS and an $FiO_2$ > 0.35 on oxyhood therapy and with compatible X-ray findings, surfactant was administered followed by mechanical ventilation |
| Outcomes | Reported in 256 neonates. The primary outcome was any requirement for mechanical ventilation between study enrolment and hospital discharge<br>The secondary outcomes were death, BPD, death/BPD, use of surfactant, pneumothorax, IVH (grade III or IV), patent ductus arteriosus (PDA), late-onset sepsis, retinopathy of prematurity (ROP) and nasal damage |
| Notes | CPAP equipment was donated by Fisher & Paykel Healthcare, Inc |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | A computerized randomisation system was used.<br>The infants were stratified by birth weight (800 to 999 grams and 1000 to 1500 grams) and by centre |
| Allocation concealment (selection bias) | Low risk | Allocation obscured in a sealed opaque envelope. |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Not possible to blind staff who had to apply either CPAP or intubation |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Complete follow-up. |
| Selective reporting (reporting bias) | Low risk | Protocol available. All of the study's prespecified outcomes have been reported |
| Other bias | Low risk | Trial was prospectively registered. |


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**Gonçalves-Ferri 2014**

| | |
|---|---|
| Methods | Multicentre randomised controlled trial involving 5 public university hospitals from June 2008 to December 2009. The infants were stratified according to birth weight (1000 to 1250 grams and 1251 to 1500 grams) in blocks of four and the cards were placed in opaque sealed envelopes |
| Participants | 250 infants who were eligible for the study. 59 were excluded of which informed consent for 42 not obtained on time, 10 because their CPAP was not ready on time and 7 infants' parents refused to participate. Premature infants with a birth weight of 1000 to 1500 grams without major malformations or foetal hydrops. Only the first twin was included. These infants were not intubated or extubated in less than 15 minutes after birth |
| Interventions | Experiment Group: Positive pressure was applied using a Neopuff manual ventilator with a PEEP at 5 $cmH_2O$ and 100% oxygen. Newborns were transferred to the Neonatal Intensive Care Unit where, after stabilization, ventilation parameters followed institutional protocols. The CPAP group was maintained with positive pressure for at least 48 hours<br>Control group: Infants who presented with central cyanosis, oxygen was started according to the techniques recommended by the guidelines of the AAP and AHA. According to the study protocol infants in the control group who failed supportive therapy were to be administered CPAP prior to the use of mechanical ventilation |
| Outcomes | A total of 256 infants were considered eligible of which 197 patients were included in the study. The primary outcomes were the need for mechanical ventilation or surfactant, or both, during the first 5 days of life; and the secondary outcomes were the incidence of respiratory morbidity and mortality during the hospital stay |
| Notes | Funding supported by FAPESP #2006/61388-2. Clarification on method allocation and measurement of failed treatment was supplied by the authors along with data on mortality and BPD |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of random sequence generation not described. Stratified into 2 weight strata in blocks of 4 |
| Allocation concealment (selection bias) | Unclear risk | Cards placed in sealed opaque envelopes. Stratified into 2 weight strata (1000 to 1250 grams and 1251 to 1500 grams) and by centre using permuted blocks of 4 at a 1:1 ratio for intervention and control<br>Comment: since there was no blinding of the intervention and blocks of 4 were used, there is a possibility that the allocated intervention of each 4th infant could have been known prior to allocation |


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| | | |
|---|---|---|
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Family members not blinded. Not feasible to blind medical staff administering the treatment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No loss of participants to follow-up. |
| Selective reporting (reporting bias) | Low risk | Limited protocol available on trials registration document. All of the study's pre-specified outcomes have been reported. Mortality was not included in the protocol but was reported in the clinical report. Comment: however since there was no reported difference in mortality we don't suspect selective reporting of this outcome |
| Other bias | Low risk | None detected. |

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

| Study | Reason for exclusion |
|---|---|
| Drew 1982 | This study examined elective intubation at birth followed by CPAP via the endotracheal tube vs selective intubation on clinical grounds |
| Rojas 2009 | Infants were randomly assigned at between 15 and 60 minutes of birth and nasal CPAP was compared with INSURE |
| Thomson 2002 | Study only available in abstract form. This study was a multi-centre RCT on prophylactic CPAP with 4 arms and 237 participants. Two groups received prophylactic CPAP (one with and one without prophylactic surfactant) and the authors state that in the two groups of infants, early nasal CPAP with prophylactic surfactant (group 1), early nasal CPAP +/- rescue surfactant (group 2), 76% and 79% of the participants were on prophylactic CPAP by 6 hours of life. Therefore it is highly unlikely that this study meets our inclusion criteria of prophylactic CPAP starting within 15 minutes of life |
| Tooley 2003 | This study examined preterm babies with RDS who were electively intubated and given one dose of surfactant within 20 minutes or less after birth. These infants were then randomised to either continue with mechanical ventilation or to be extubated to nasal CPAP within one hour after birth. The inclusion criteria required the intervention to be started within 15 minutes of life |
| Zaharie 2008 | This was an observational study examining preterm babies between 28 and 32 weeks' gestational age who were given either early or prophylactic CPAP. There was no blinding or randomisation |


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## DATA AND ANALYSES

### Comparison 1. Prophylactic CPAP vs supportive care

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Failed Treatment | 4 | 765 | Risk Difference (M-H, Random, 95% CI) | -0.16 [-0.34, 0.02] |
| 1.1 Birth weight ≥ 1000 grams | 4 | 716 | Risk Difference (M-H, Random, 95% CI) | -0.12 [-0.32, 0.07] |
| 1.2 Birth weight < 1000 grams | 1 | 49 | Risk Difference (M-H, Random, 95% CI) | -0.35 [-0.58, -0.11] |
| 2 Bronchopulmonary dysplasia at 28 days | 3 | 535 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.77, 1.36] |
| 2.1 Birth weight ≥ 1000 grams | 3 | 486 | Risk Ratio (M-H, Random, 95% CI) | 1.18 [0.73, 1.92] |
| 2.2 Birth weight < 1000 grams | 1 | 49 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.65, 1.27] |
| 3 Bronchopulmonary dysplasia at 28 days | 2 | 338 | Risk Ratio (M-H, Random, 95% CI) | 1.23 [0.51, 2.96] |
| 3.1 Antenatal steroids | 1 | 256 | Risk Ratio (M-H, Random, 95% CI) | 0.90 [0.71, 1.13] |
| 3.2 No antenatal steroids | 1 | 82 | Risk Ratio (M-H, Random, 95% CI) | 2.27 [0.77, 6.65] |
| 4 Bronchopulmonary dysplasia at 36 weeks | 3 | 683 | Risk Ratio (M-H, Random, 95% CI) | 0.79 [0.50, 1.24] |
| 4.1 Birth weight ≥ 1000 grams | 3 | 634 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.37, 1.60] |
| 4.2 Birth weight < 1000 grams | 1 | 49 | Risk Ratio (M-H, Random, 95% CI) | 0.90 [0.47, 1.71] |
| 5 Neonatal death | 4 | 765 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.56, 1.93] |
| 5.1 Birth weight ≥ 1000 grams | 4 | 716 | Risk Ratio (M-H, Random, 95% CI) | 1.00 [0.46, 2.17] |
| 5.2 Birth weight < 1000 grams | 1 | 49 | Risk Ratio (M-H, Random, 95% CI) | 1.22 [0.39, 3.79] |
| 6 Death or bronchopulmonary dysplasia | 1 | 256 | Risk Ratio (M-H, Fixed, 95% CI) | 0.69 [0.40, 1.19] |
| 6.1 Birth weight ≥ 1000 grams | 1 | 207 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.29, 1.30] |
| 6.2 Birth weight < 1000 grams | 1 | 49 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.37, 1.82] |
| 7 Use of surfactant | 3 | 683 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.58, 0.96] |
| 7.1 Birth weight > 1000 grams | 3 | 634 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.61, 1.05] |
| 7.2 Birth weight < 1000 grams | 1 | 49 | Risk Ratio (M-H, Fixed, 95% CI) | 0.51 [0.29, 0.89] |
| 8 Pneumothorax | 3 | 568 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.35, 1.61] |
| 9 Local Trauma | 2 | | Risk Difference (M-H, Random, 95% CI) | Subtotals only |
| 9.1 Subglottic stenosis | 1 | 82 | Risk Difference (M-H, Random, 95% CI) | -0.03 [-0.09, 0.04] |
| 9.2 Nasal injury | 1 | 256 | Risk Difference (M-H, Random, 95% CI) | 0.08 [0.03, 0.13] |
| 10 IVH (any grade) | 2 | 338 | Risk Ratio (M-H, Fixed, 95% CI) | 1.42 [0.94, 2.13] |
| 11 IVH grade 3 or 4 | 2 | 486 | Risk Ratio (M-H, Fixed, 95% CI) | 0.96 [0.39, 2.37] |
| 12 Periventricular leukomalacia | 1 | 230 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.04, 3.16] |
| 13 Necrotizing enterocolitis | 3 | 568 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.55, 1.50] |
| 14 Sepsis | 3 | 568 | Risk Ratio (M-H, Fixed, 95% CI) | 1.04 [0.64, 1.69] |
| 15 Retinopathy of prematurity grade 3 or 4 | 2 | 312 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.13, 3.32] |


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**Comparison 2. Prophylactic CPAP vs assisted ventilation**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Bronchopulmonary dysplasia (BPD) at 28 days | 1 | 610 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.70, 0.94] |
| 2 Bronchopulmonary dysplasia at 36 weeks | 3 | 2150 | Risk Difference (M-H, Fixed, 95% CI) | -0.04 [-0.08, -0.00] |
| 2.1 Gestation < 28 weeks | 3 | 1918 | Risk Difference (M-H, Fixed, 95% CI) | -0.05 [-0.09, -0.01] |
| 2.2 Gestation ≥ 28 weeks | 1 | 232 | Risk Difference (M-H, Fixed, 95% CI) | 0.02 [-0.08, 0.12] |
| 3 Bronchopulmonary dysplasia at 36 weeks | 3 | 2150 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.79, 0.99] |
| 3.1 CPAP started at 5 $cmH_2O$ | 2 | 1540 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.80, 1.03] |
| 3.2 CPAP started at 8 $cmH_2O$ | 1 | 610 | Risk Ratio (M-H, Fixed, 95% CI) | 0.83 [0.65, 1.06] |
| 4 Neonatal Death | 3 | 2358 | Risk Ratio (M-H, Fixed, 95% CI) | 0.82 [0.66, 1.03] |
| 4.1 CPAP started at 5 $cmH_2O$ | 2 | 1748 | Risk Ratio (M-H, Fixed, 95% CI) | 0.78 [0.62, 0.99] |
| 4.2 CPAP started at 8 $cmH_2O$ | 1 | 610 | Risk Ratio (M-H, Fixed, 95% CI) | 1.10 [0.59, 2.03] |
| 5 Neonatal Death | 3 | 2358 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.66, 1.03] |
| 5.1 Gestation < 28 weeks | 3 | 2126 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.66, 1.04] |
| 5.2 Gestation ≥ 28 weeks | 1 | 232 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.16, 3.01] |
| 6 Death or bronchopulmonary dysplasia | 3 | 2358 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.81, 0.97] |
| 6.1 CPAP started at 5 $cmH_2O$ | 2 | 1748 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.81, 0.98] |
| 6.2 CPAP started at 8 $cmH_2O$ | 1 | 610 | Risk Ratio (M-H, Fixed, 95% CI) | 0.87 [0.70, 1.07] |
| 7 Death or Bronchopulmonary dysplasia | 3 | 2358 | Odds Ratio (M-H, Random, 95% CI) | 0.80 [0.68, 0.94] |
| 7.1 Gestation < 28 weeks | 3 | 2126 | Odds Ratio (M-H, Random, 95% CI) | 0.78 [0.66, 0.93] |
| 7.2 Gestation ≥ 28 weeks | 1 | 232 | Odds Ratio (M-H, Random, 95% CI) | 1.04 [0.56, 1.94] |
| 8 Assisted ventilation | 2 | 1042 | Risk Difference (M-H, Random, 95% CI) | -0.49 [-0.59, -0.39] |
| 8.1 CPAP started at 5 $cmH_2O$ | 1 | 432 | Risk Difference (M-H, Random, 95% CI) | -0.44 [-0.51, -0.37] |
| 8.2 CPAP started at 8 $cmH_2O$ | 1 | 610 | Risk Difference (M-H, Random, 95% CI) | -0.54 [-0.60, -0.48] |
| 9 Use of surfactant | 3 | 2354 | Risk Ratio (M-H, Random, 95% CI) | 0.54 [0.40, 0.73] |
| 9.1 CPAP started at 5 $cmH_2O$ | 2 | 1744 | Risk Ratio (M-H, Random, 95% CI) | 0.56 [0.37, 0.84] |
| 9.2 CPAP started at 8 $cmH_2O$ | 1 | 610 | Risk Ratio (M-H, Random, 95% CI) | 0.49 [0.42, 0.57] |
| 10 Pneumothorax | 3 | 2357 | Risk Ratio (M-H, Fixed, 95% CI) | 1.24 [0.91, 1.69] |
| 10.1 CPAP started at 5 $cmH_2O$ | 2 | 1747 | Risk Ratio (M-H, Fixed, 95% CI) | 0.96 [0.67, 1.37] |
| 10.2 CPAP started at 8 $cmH_2O$ | 1 | 610 | Risk Ratio (M-H, Fixed, 95% CI) | 3.07 [1.47, 6.40] |
| 11 IVH (any grade) | 1 | 421 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.66, 1.36] |


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| | | | | |
|---|---|---|---|---|
| 12 IVH grade 3 or 4 | 3 | 2301 | Risk Ratio (M-H, Fixed, 95% CI) | 1.09 [0.86, 1.39] |
| 13 Periventricular leukomalacia | 2 | 1006 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.39, 1.79] |
| 14 Necrotizing enterocolitis | 3 | 2331 | Risk Ratio (M-H, Fixed, 95% CI) | 1.19 [0.92, 1.55] |
| 15 Sepsis | 1 | 425 | Risk Ratio (M-H, Random, 95% CI) | 0.59 [0.33, 1.04] |
| 16 Retinopathy of prematurity grade 3 or 4 | 2 | 1359 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.77, 1.39] |

### Analysis 1.1. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 1 Failed Treatment.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 1 Failed Treatment

| Study or subgroup | CPAP n/N | Supportive Care n/N | Risk Difference M-H,Random,95% CI | Weight | Risk Difference M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Birth weight ≥ 1000 grams | | | | | |
| Han 1987 | 17/43 | 12/39 | | 18.1 % | 0.09 [ -0.12, 0.29 ] |
| Sandri 2004 | 14/115 | 14/115 | | 22.7 % | 0.0 [ -0.08, 0.08 ] |
| Tapia 2012 | 25/104 | 43/103 | | 21.3 % | -0.18 [ -0.30, -0.05 ] |
| Gon˙x00e7˙alves˙x002d˙Ferri 2014 | 23/98 | 60/99 | | 21.2 % | -0.37 [ -0.50, -0.24 ] |
| **Subtotal (95% CI)** | **360** | **356** | | **83.3 %** | **-0.12 [ -0.32, 0.07 ]** |
| Total events: 79 (CPAP), 129 (Supportive Care) | | | | | |
| Heterogeneity: $Tau^2$ = 0.03; $Chi^2$ = 28.42, df = 3 (P<0.00001); $I^2$ =89% | | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | | |
| 2 Birth weight < 1000 grams | | | | | |
| Tapia 2012 | 14/27 | 19/22 | | 16.7 % | -0.35 [ -0.58, -0.11 ] |
| **Subtotal (95% CI)** | **27** | **22** | | **16.7 %** | **-0.35 [ -0.58, -0.11 ]** |
| Total events: 14 (CPAP), 19 (Supportive Care) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.86 (P = 0.0043) | | | | | |
| **Total (95% CI)** | **387** | **378** | | **100.0 %** | **-0.16 [ -0.34, 0.02 ]** |
| Total events: 93 (CPAP), 148 (Supportive Care) | | | | | |
| Heterogeneity: $Tau^2$ = 0.03; $Chi^2$ = 31.97, df = 4 (P<0.00001); $I^2$ =87% | | | | | |
| Test for overall effect: Z = 1.76 (P = 0.079) | | | | | |
| Test for subgroup differences: $Chi^2$ = 2.05, df = 1 (P = 0.15), $I^2$ =51% | | | | | |



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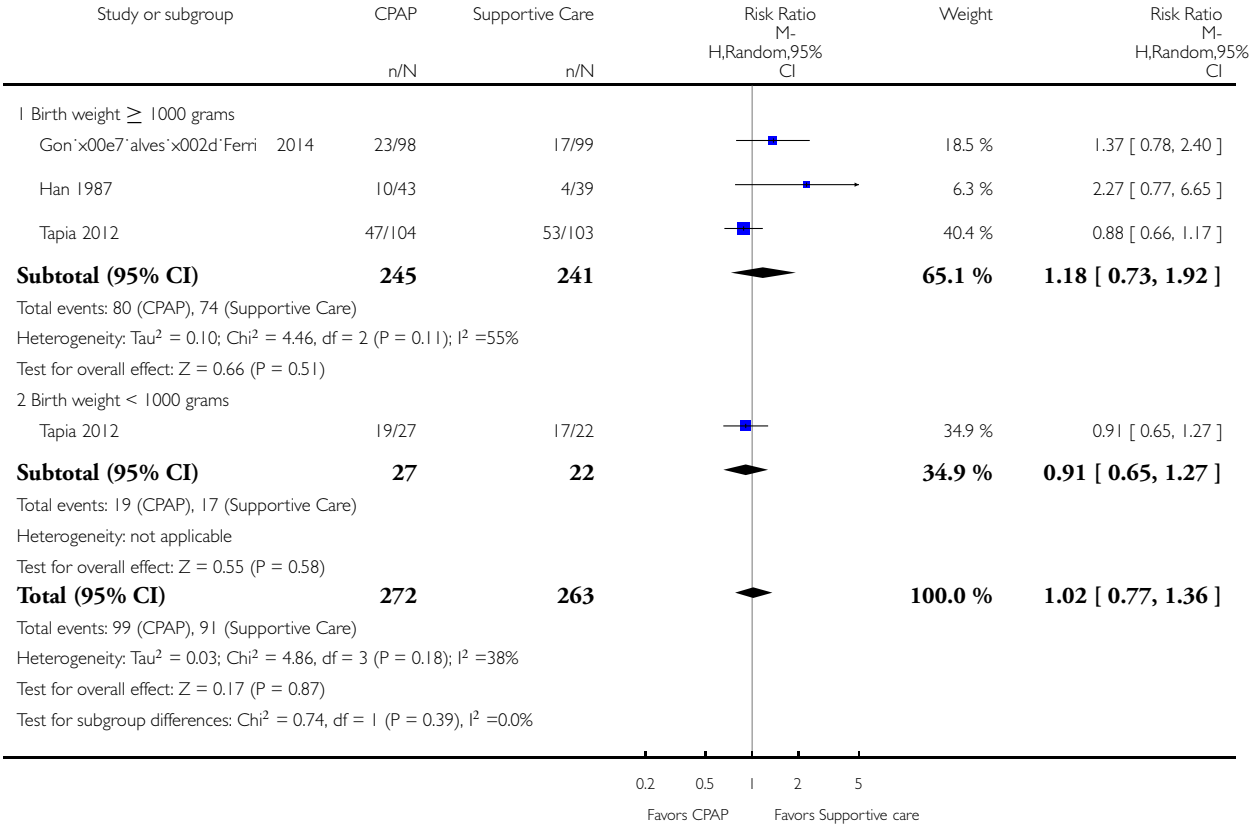
## Analysis 1.2. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 2 Bronchopulmonary dysplasia at 28 days.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 2 Bronchopulmonary dysplasia at 28 days





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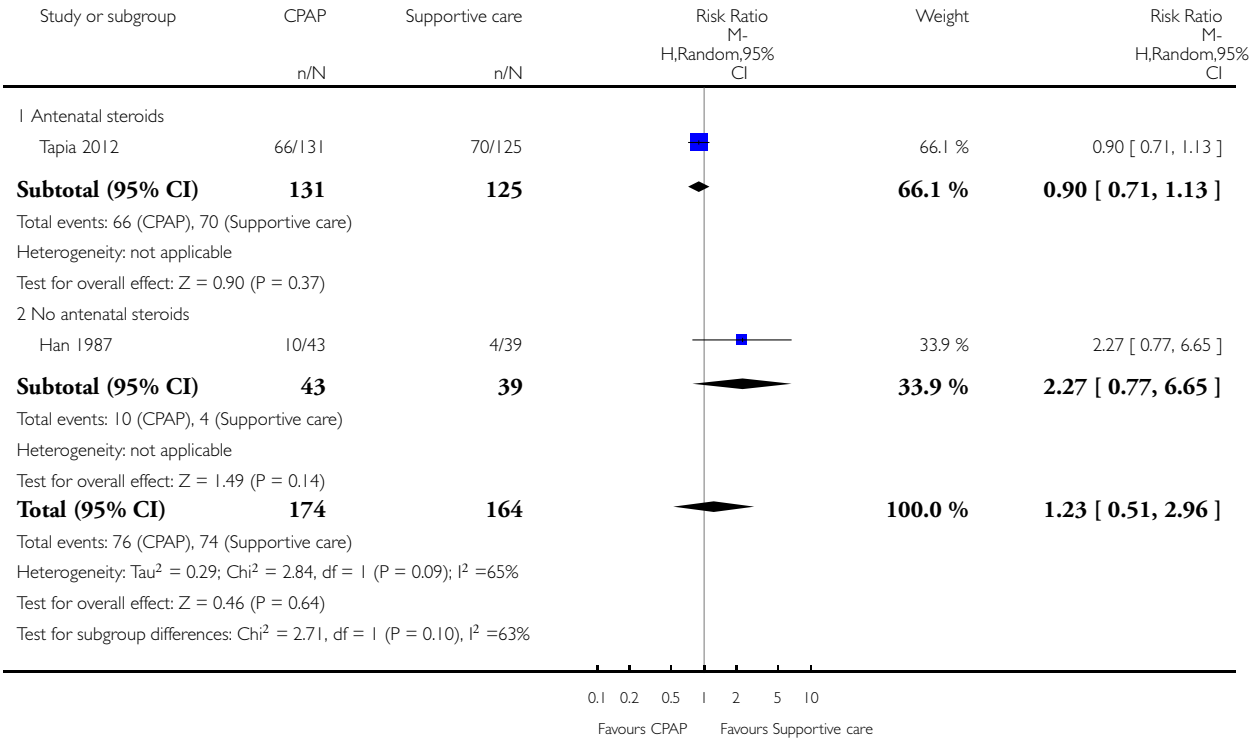
## Analysis 1.3. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 3 Bronchopulmonary dysplasia at 28 days.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 3 Bronchopulmonary dysplasia at 28 days





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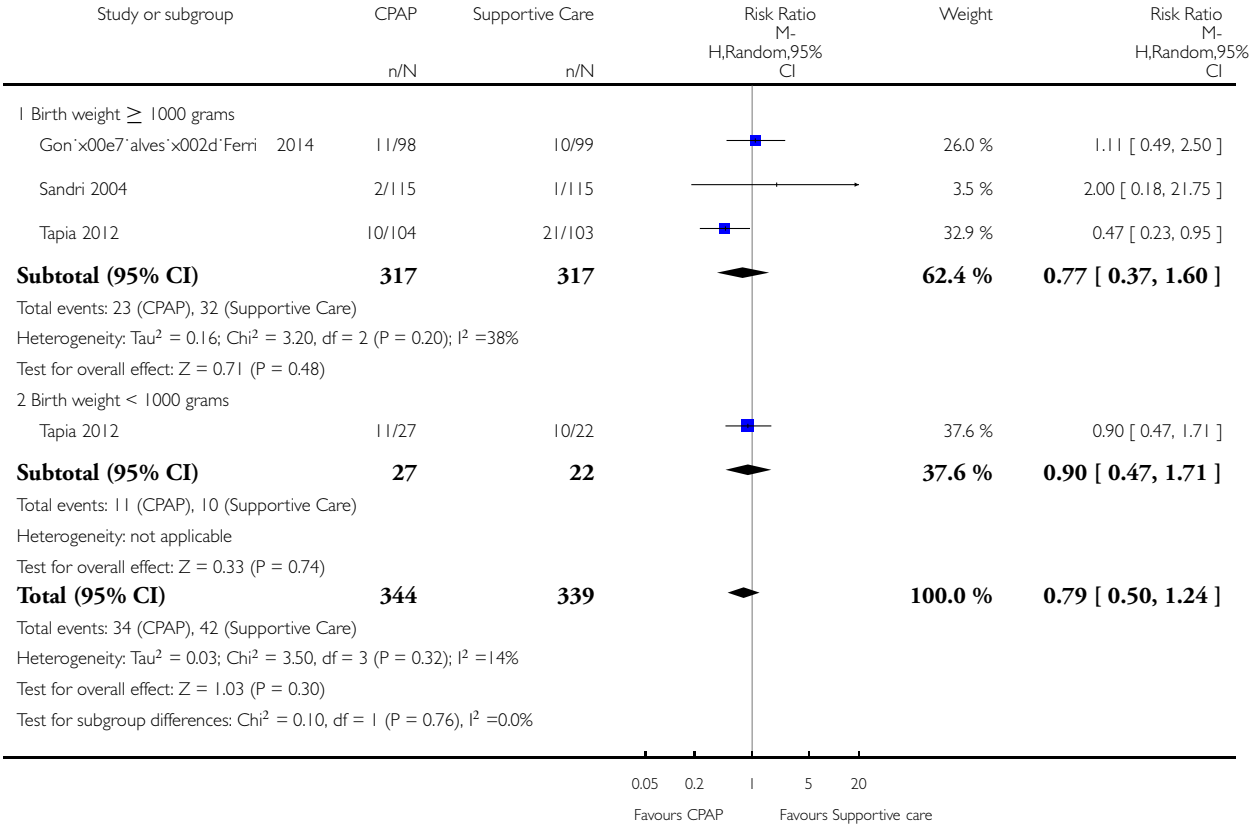
## Analysis 1.4. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 4 Bronchopulmonary dysplasia at 36 weeks.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 4 Bronchopulmonary dysplasia at 36 weeks





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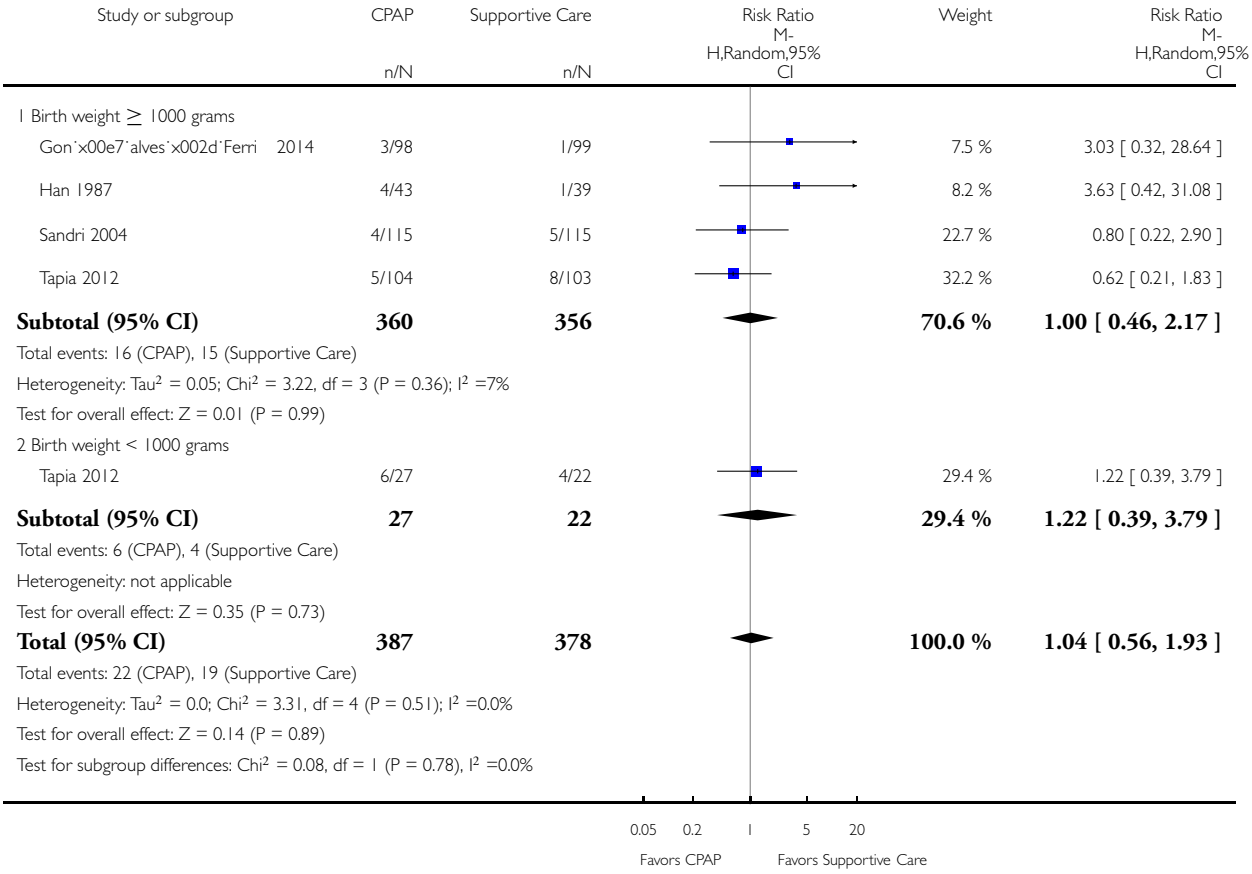
## Analysis 1.5. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 5 Neonatal death.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 5 Neonatal death





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## Analysis 1.6. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 6 Death or bronchopulmonary dysplasia.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 6 Death or bronchopulmonary dysplasia

| Study or subgroup | CPAP n/N | Supportive Care n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Birth weight ≥ 1000 grams | | | | | |
| Tapia 2012 | 10/104 | 16/103 | | 64.6 % | 0.62 [ 0.29, 1.30 ] |
| **Subtotal (95% CI)** | **104** | **103** | | **64.6 %** | **0.62 [ 0.29, 1.30 ]** |
| Total events: 10 (CPAP), 16 (Supportive Care) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.27 (P = 0.20) | | | | | |
| 2 Birth weight < 1000 grams | | | | | |
| Tapia 2012 | 8/27 | 8/22 | | 35.4 % | 0.81 [ 0.37, 1.82 ] |
| **Subtotal (95% CI)** | **27** | **22** | | **35.4 %** | **0.81 [ 0.37, 1.82 ]** |
| Total events: 8 (CPAP), 8 (Supportive Care) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.50 (P = 0.62) | | | | | |
| **Total (95% CI)** | **131** | **125** | | **100.0 %** | **0.69 [ 0.40, 1.19 ]** |
| Total events: 18 (CPAP), 24 (Supportive Care) | | | | | |
| Heterogeneity: $Chi^2$ = 0.25, df = 1 (P = 0.62); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.18) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.24, df = 1 (P = 0.62), $I^2$ =0.0% | | | | | |



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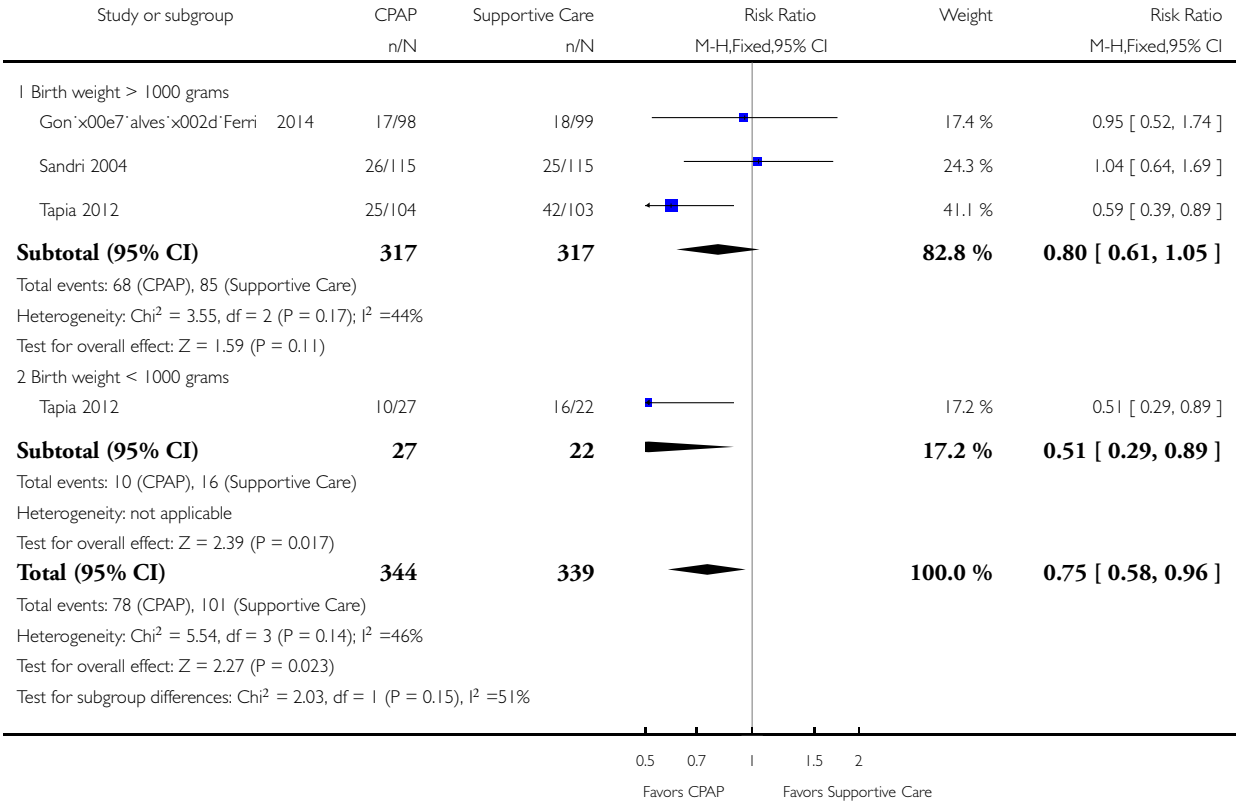
## Analysis 1.7. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 7 Use of surfactant.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 7 Use of surfactant





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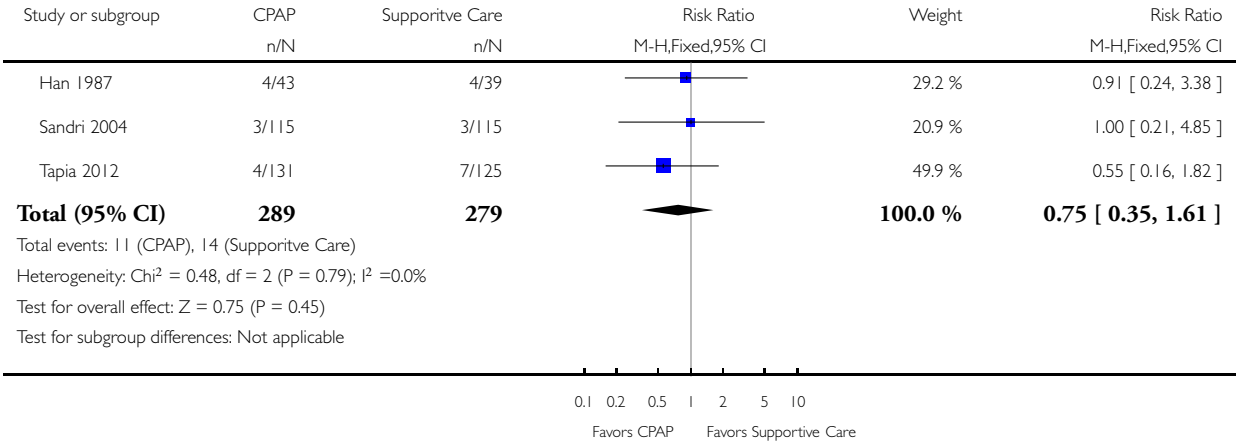
### Analysis 1.8. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 8 Pneumothorax.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 8 Pneumothorax





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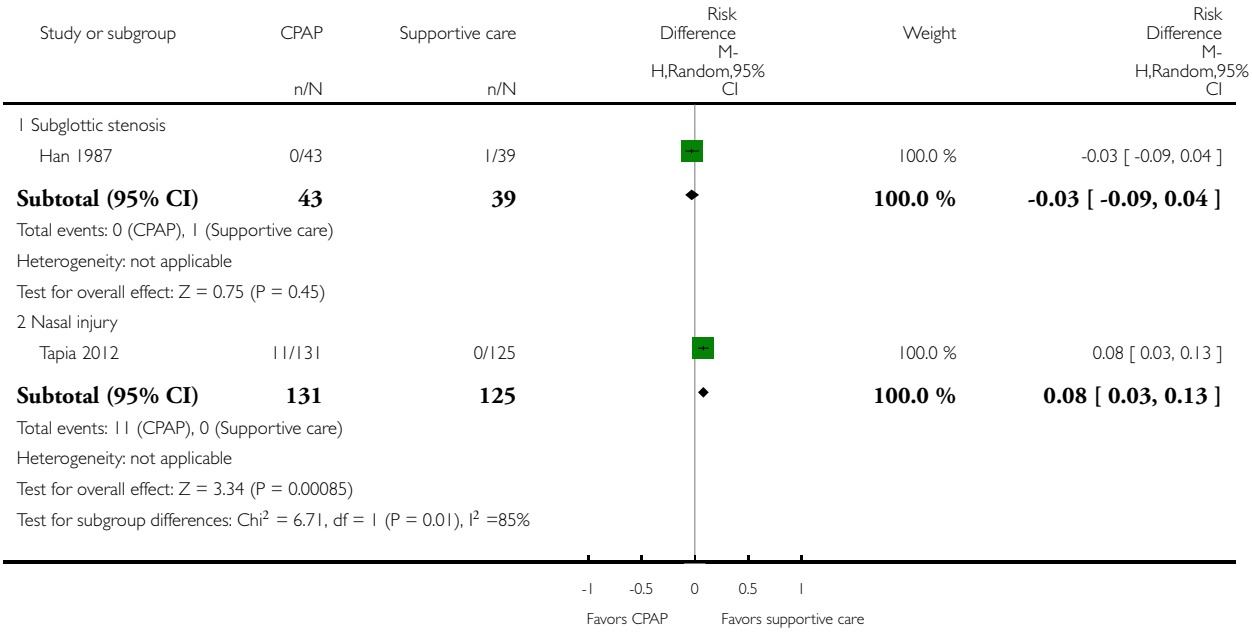
### Analysis 1.9. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 9 Local Trauma.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 9 Local Trauma





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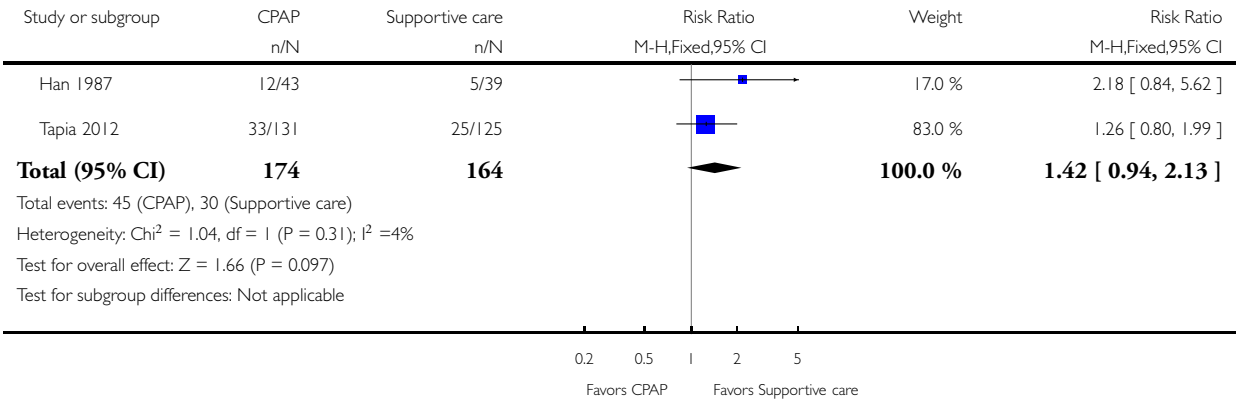
### Analysis 1.10. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 10 IVH (any grade).

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 10 IVH (any grade)

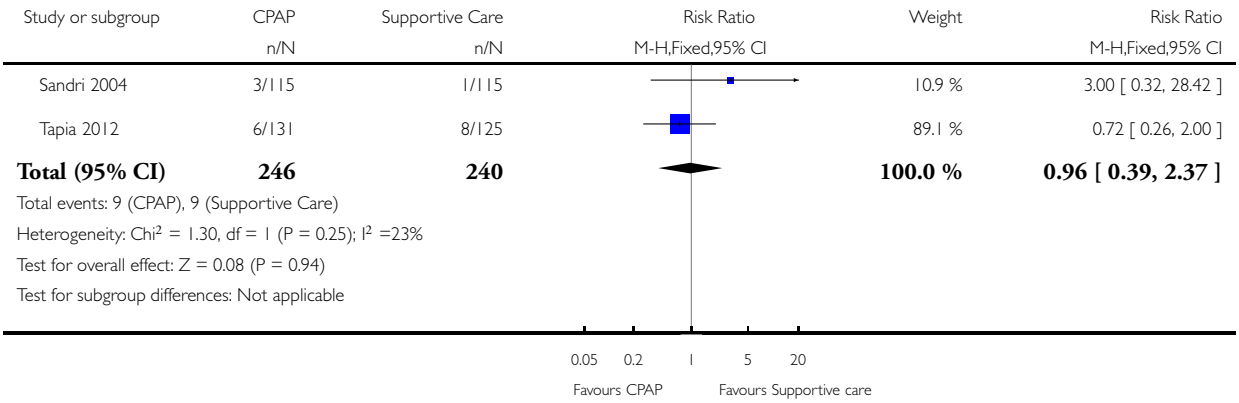



### Analysis 1.11. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 11 IVH grade 3 or 4.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 11 IVH grade 3 or 4





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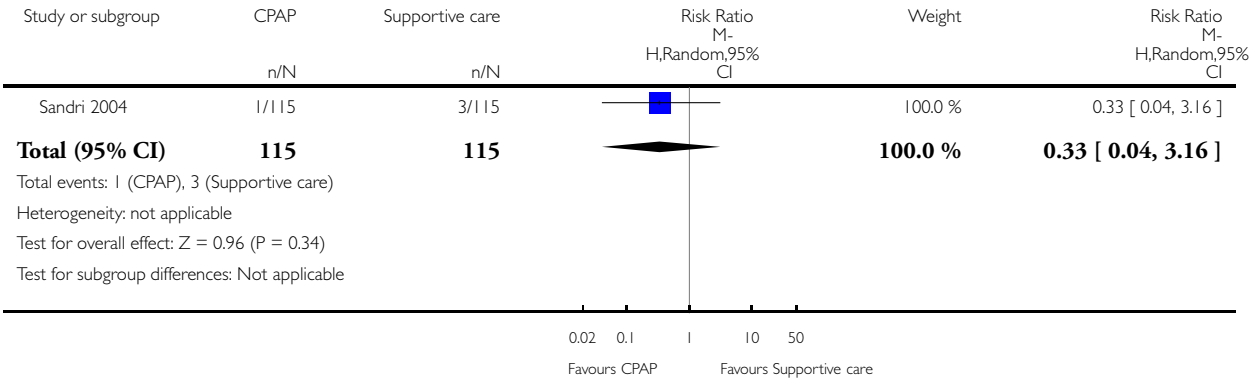
### Analysis 1.12. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 12 Periventricular leukomalacia.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 12 Periventricular leukomalacia

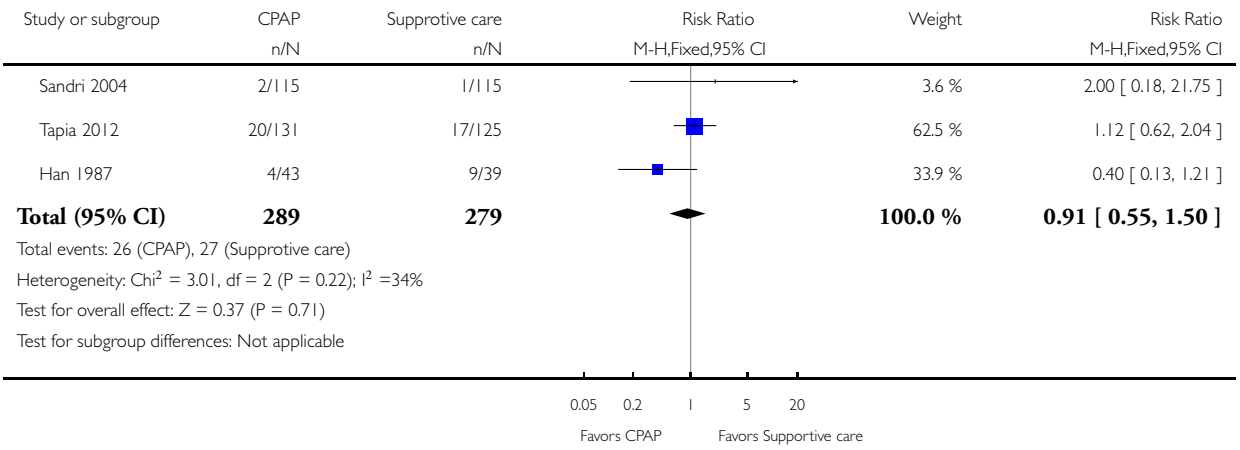



### Analysis 1.13. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 13 Necrotizing enterocolitis.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 13 Necrotizing enterocolitis





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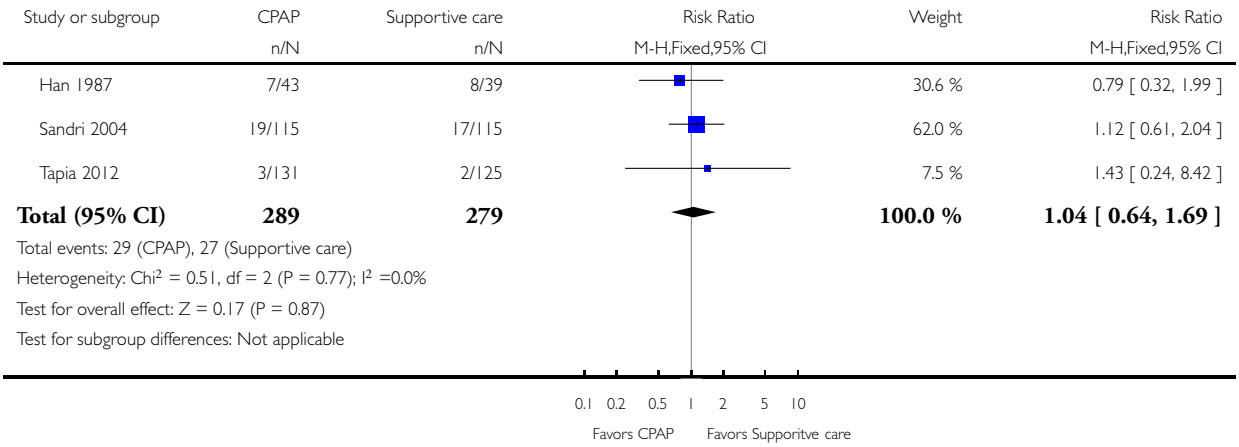
### Analysis 1.14. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 14 Sepsis.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 14 Sepsis





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### Analysis 1.15. Comparison 1 Prophylactic CPAP vs supportive care, Outcome 15 Retinopathy of prematurity grade 3 or 4.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 1 Prophylactic CPAP vs supportive care

Outcome: 15 Retinopathy of prematurity grade 3 or 4

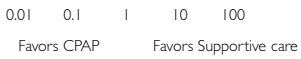
| Study or subgroup | CPAP n/N | Supportive care n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Han 1987 | 2/43 | 2/39 | | 58.3 % | 0.91 [ 0.13, 6.13 ] |
| Sandri 2004 | 0/115 | 1/115 | | 41.7 % | 0.33 [ 0.01, 8.10 ] |
| **Total (95% CI)** | **158** | **154** | | **100.0 %** | **0.67 [ 0.13, 3.32 ]** |

Total events: 2 (CPAP), 3 (Supportive care)

Heterogeneity: $Chi^2 = 0.28$, df = 1 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 0.49 (P = 0.62)

Test for subgroup differences: Not applicable




### Analysis 2.1. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 1 Bronchopulmonary dysplasia (BPD) at 28 days.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 1 Bronchopulmonary dysplasia (BPD) at 28 days

| Study or subgroup | CPAP n/N | Assisted Ventilat n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Morley 2008 | 149/307 | 181/303 | | 100.0 % | 0.81 [ 0.70, 0.94 ] |
| **Total (95% CI)** | **307** | **303** | | **100.0 %** | **0.81 [ 0.70, 0.94 ]** |

Total events: 149 (CPAP), 181 (Assisted Ventilat)

Heterogeneity: not applicable

Test for overall effect: Z = 2.76 (P = 0.0059)

Test for subgroup differences: Not applicable



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## Analysis 2.2. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 2 Bronchopulmonary dysplasia at 36 weeks.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 2 Bronchopulmonary dysplasia at 36 weeks

| Study or subgroup | CPAP n/N | Assisted Ventilation n/N | Risk Difference M-H,Fixed,95% CI | Weight | Risk Difference M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Gestation < 28 weeks | | | | | |
| Dunn 2011 | 35/102 | 41/98 | | 9.3 % | -0.08 [ -0.21, 0.06 ] |
| Finer 2010 | 229/569 | 239/539 | | 51.5 % | -0.04 [ -0.10, 0.02 ] |
| Morley 2008 | 84/307 | 100/303 | | 28.4 % | -0.06 [ -0.13, 0.02 ] |
| **Subtotal (95% CI)** | **978** | **940** | | **89.2 %** | **-0.05 [ -0.09, -0.01 ]** |
| Total events: 348 (CPAP), 380 (Assisted Ventilation) | | | | | |
| Heterogeneity: $Chi^2$ = 0.26, df = 2 (P = 0.88); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.25 (P = 0.025) | | | | | |
| 2 Gestation ≥ 28 weeks | | | | | |
| Dunn 2011 | 24/121 | 20/111 | | 10.8 % | 0.02 [ -0.08, 0.12 ] |
| **Subtotal (95% CI)** | **121** | **111** | | **10.8 %** | **0.02 [ -0.08, 0.12 ]** |
| Total events: 24 (CPAP), 20 (Assisted Ventilation) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.72) | | | | | |
| **Total (95% CI)** | **1099** | **1051** | | **100.0 %** | **-0.04 [ -0.08, 0.00 ]** |
| Total events: 372 (CPAP), 400 (Assisted Ventilation) | | | | | |
| Heterogeneity: $Chi^2$ = 1.76, df = 3 (P = 0.62); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.07 (P = 0.039) | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.46, df = 1 (P = 0.23), $I^2$ =32% | | | | | |



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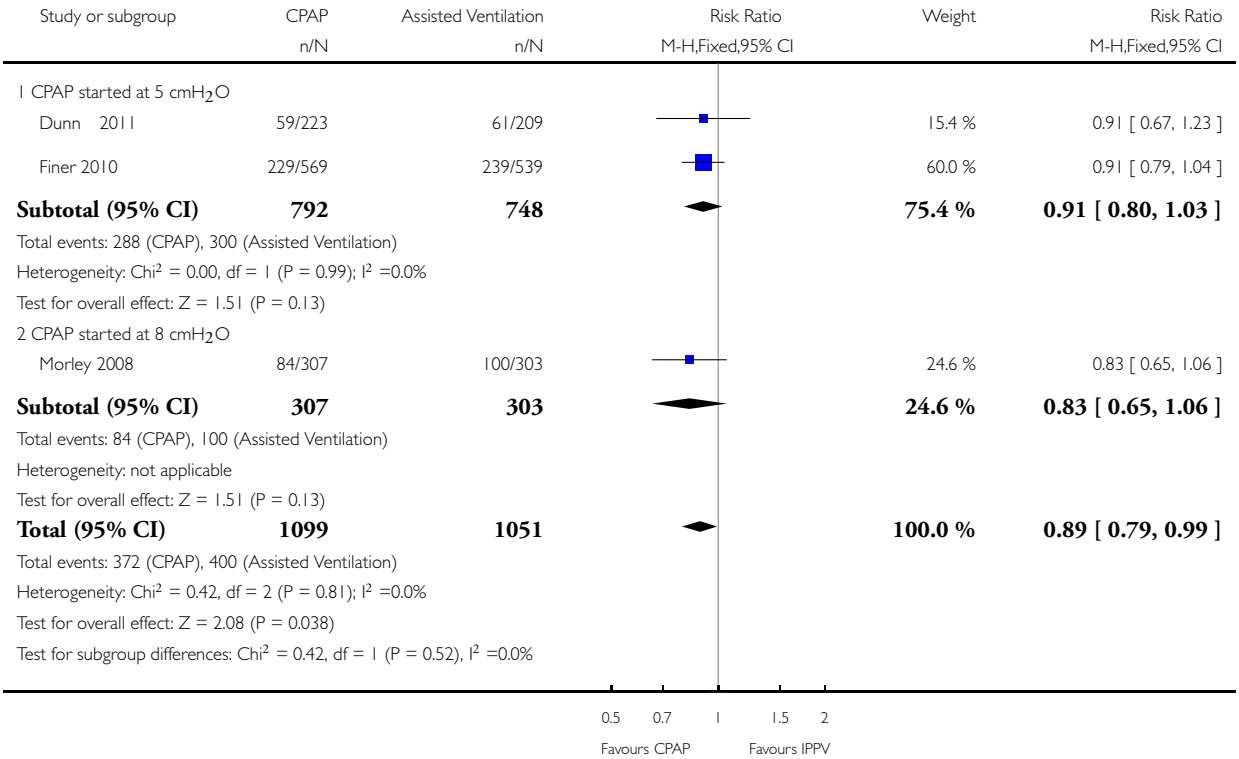
## Analysis 2.3. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 3 Bronchopulmonary dysplasia at 36 weeks.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 3 Bronchopulmonary dysplasia at 36 weeks





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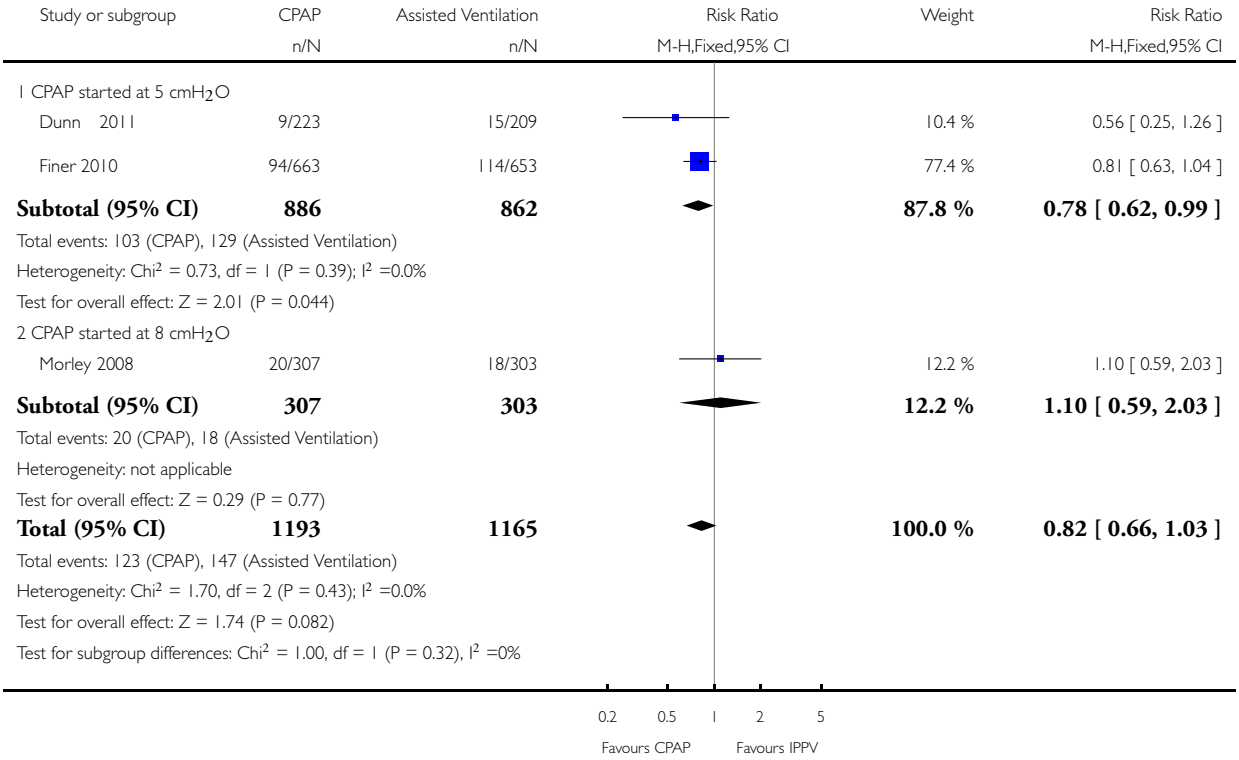
### Analysis 2.4. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 4 Neonatal Death.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 4 Neonatal Death





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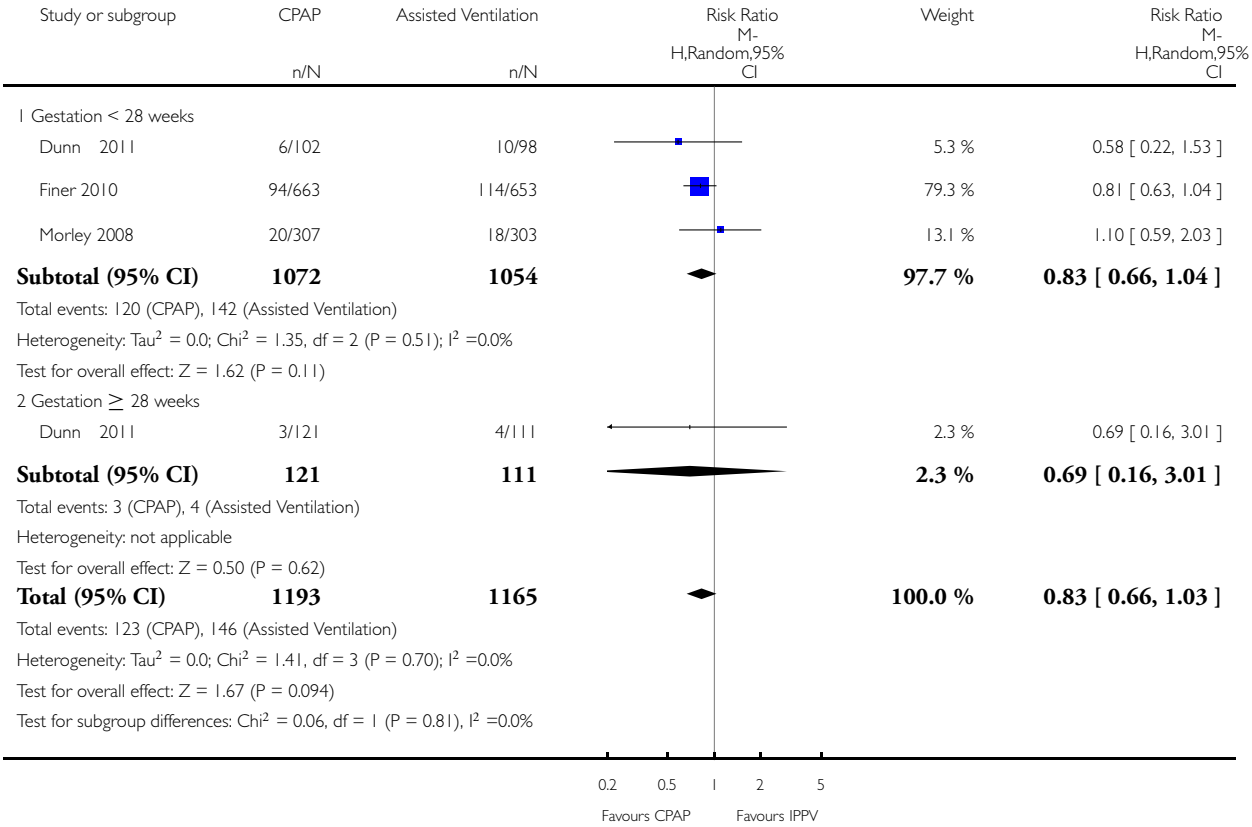
### Analysis 2.5. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 5 Neonatal Death.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 5 Neonatal Death





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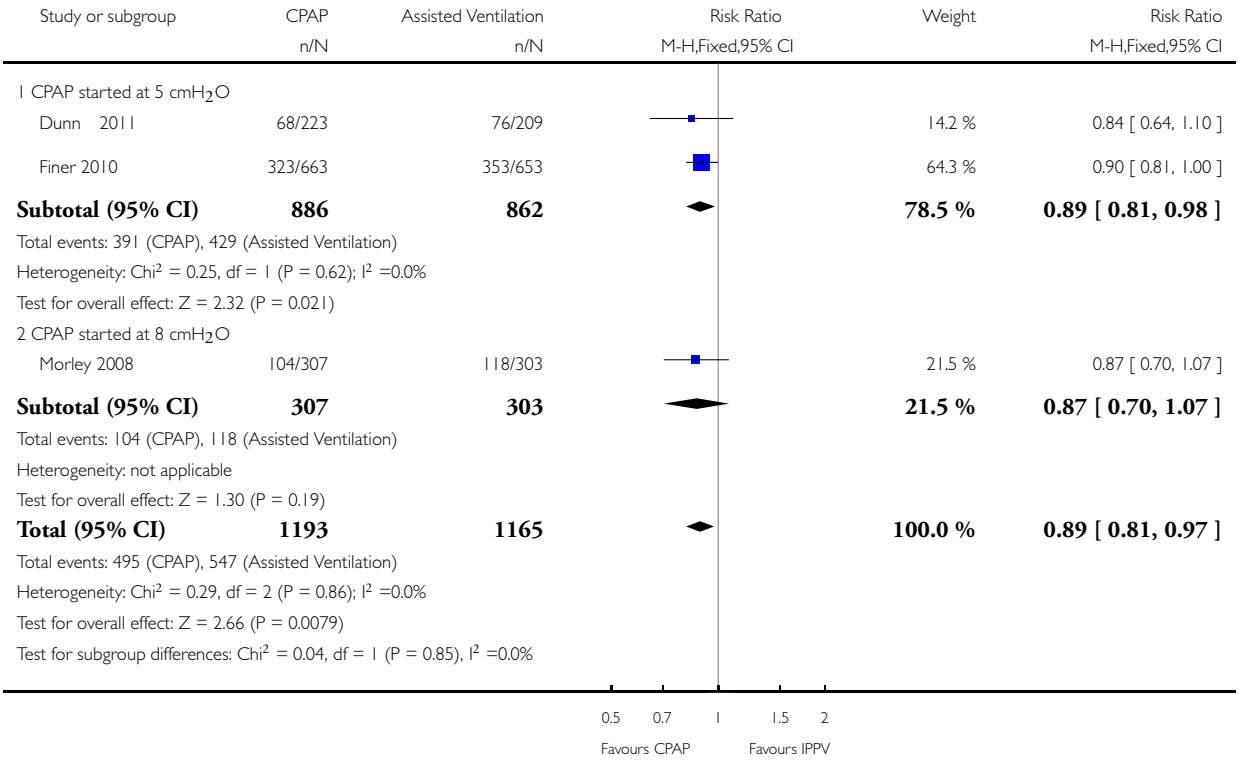
## Analysis 2.6. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 6 Death or bronchopulmonary dysplasia.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 6 Death or bronchopulmonary dysplasia





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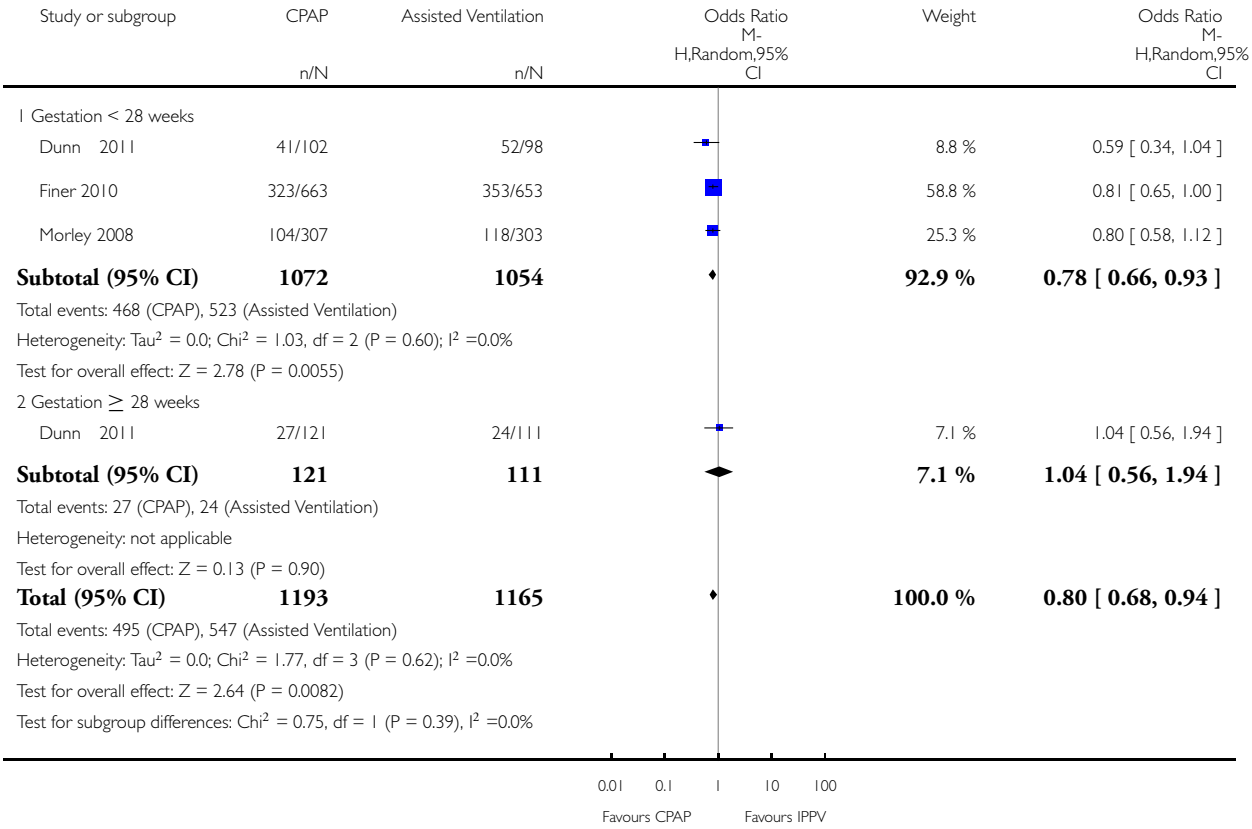
## Analysis 2.7. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 7 Death or Bronchopulmonary dysplasia.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 7 Death or Bronchopulmonary dysplasia





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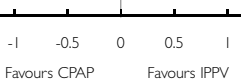
### Analysis 2.8. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 8 Assisted ventilation.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 8 Assisted ventilation

| Study or subgroup | CPAP n/N | Assisted Ventilation n/N | Risk Difference M-H,Random,95% CI | Weight | Risk Difference M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 CPAP started at 5 $cmH_2O$ | | | | | |
| Dunn 2011 | 116/223 | 200/209 | | 47.7 % | -0.44 [ -0.51, -0.37 ] |
| **Subtotal (95% CI)** | **223** | **209** | | **47.7 %** | **-0.44 [ -0.51, -0.37 ]** |
| Total events: 116 (CPAP), 200 (Assisted Ventilation) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 12.04 (P < 0.00001) | | | | | |
| 2 CPAP started at 8 $cmH_2O$ | | | | | |
| Morley 2008 | 141/307 | 303/303 | | 52.3 % | -0.54 [ -0.60, -0.48 ] |
| **Subtotal (95% CI)** | **307** | **303** | | **52.3 %** | **-0.54 [ -0.60, -0.48 ]** |
| Total events: 141 (CPAP), 303 (Assisted Ventilation) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 18.98 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **530** | **512** | | **100.0 %** | **-0.49 [ -0.59, -0.39 ]** |
| Total events: 257 (CPAP), 503 (Assisted Ventilation) | | | | | |
| Heterogeneity: $Tau^2$ = 0.00; $Chi^2$ = 5.10, df = 1 (P = 0.02); $I^2$ =80% | | | | | |
| Test for overall effect: Z = 9.44 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 5.08, df = 1 (P = 0.02), $I^2$ =80% | | | | | |





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### Analysis 2.9. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 9 Use of surfactant.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 9 Use of surfactant

| Study or subgroup | CPAP n/N | Assisted Ventilation n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 CPAP started at 5 $cmH_2O$ | | | | | |
| Dunn 2011 | 100/222 | 206/209 | | 32.7 % | 0.46 [ 0.39, 0.53 ] |
| Finer 2010 | 443/660 | 646/653 | | 35.0 % | 0.68 [ 0.64, 0.72 ] |
| **Subtotal (95% CI)** | **882** | **862** | | **67.7 %** | **0.56 [ 0.37, 0.84 ]** |
| Total events: 543 (CPAP), 852 (Assisted Ventilation) | | | | | |
| Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 26.68$, df = 1 (P<0.00001); $I^2$ =96% | | | | | |
| Test for overall effect: Z = 2.82 (P = 0.0047) | | | | | |
| 2 CPAP started at 8 $cmH_2O$ | | | | | |
| Morley 2008 | 116/307 | 233/303 | | 32.3 % | 0.49 [ 0.42, 0.57 ] |
| **Subtotal (95% CI)** | **307** | **303** | | **32.3 %** | **0.49 [ 0.42, 0.57 ]** |
| Total events: 116 (CPAP), 233 (Assisted Ventilation) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 8.91 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **1189** | **1165** | | **100.0 %** | **0.54 [ 0.40, 0.73 ]** |
| Total events: 659 (CPAP), 1085 (Assisted Ventilation) | | | | | |
| Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 40.81$, df = 2 (P<0.00001); $I^2$ =95% | | | | | |
| Test for overall effect: Z = 4.01 (P = 0.000061) | | | | | |
| Test for subgroup differences: $Chi^2 = 0.35$, df = 1 (P = 0.55), $I^2$ =0.0% | | | | | |



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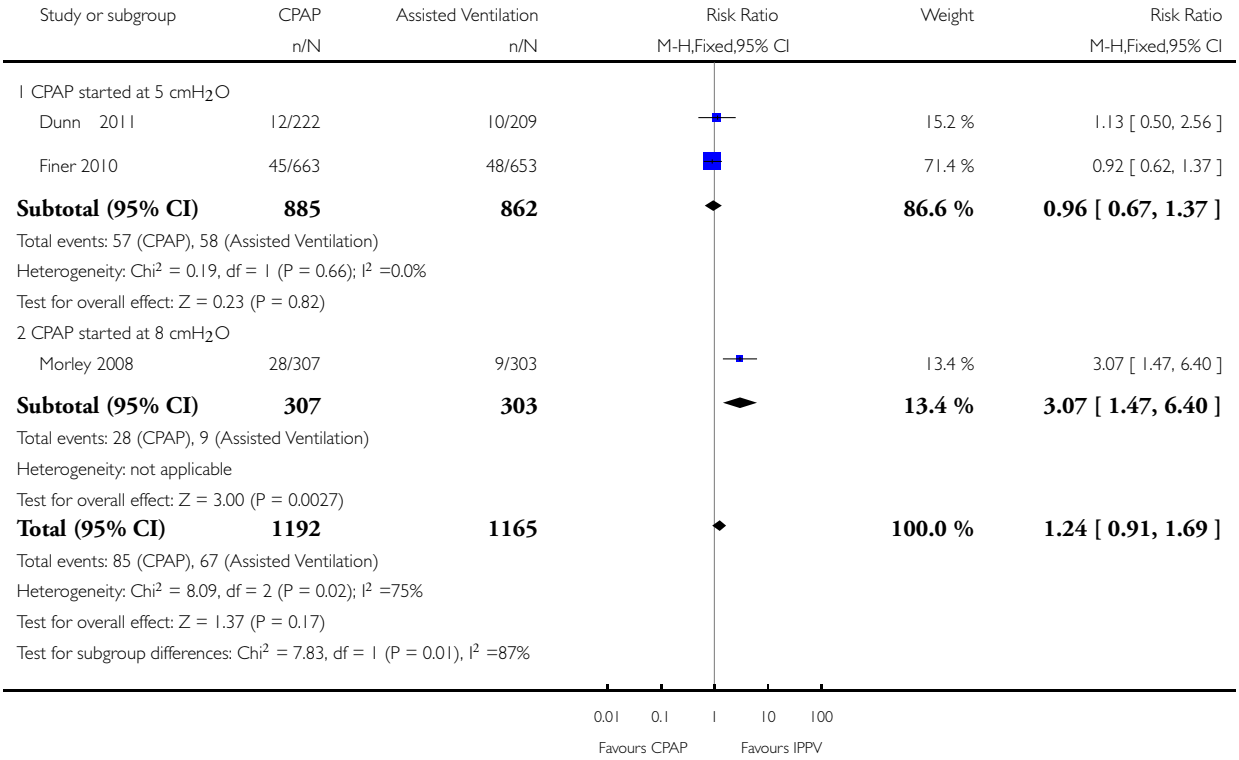
### Analysis 2.10. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 10 Pneumothorax.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 10 Pneumothorax





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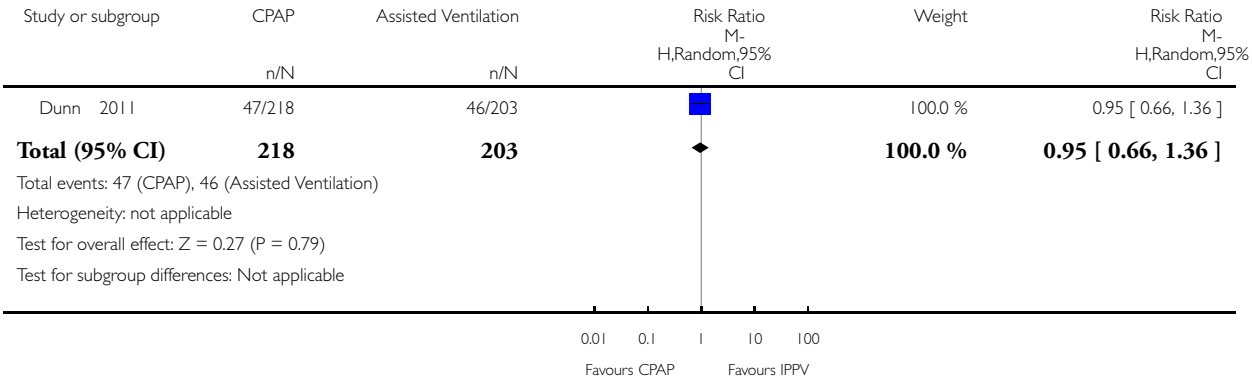
### Analysis 2.11. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 11 IVH (any grade).

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 11 IVH (any grade)

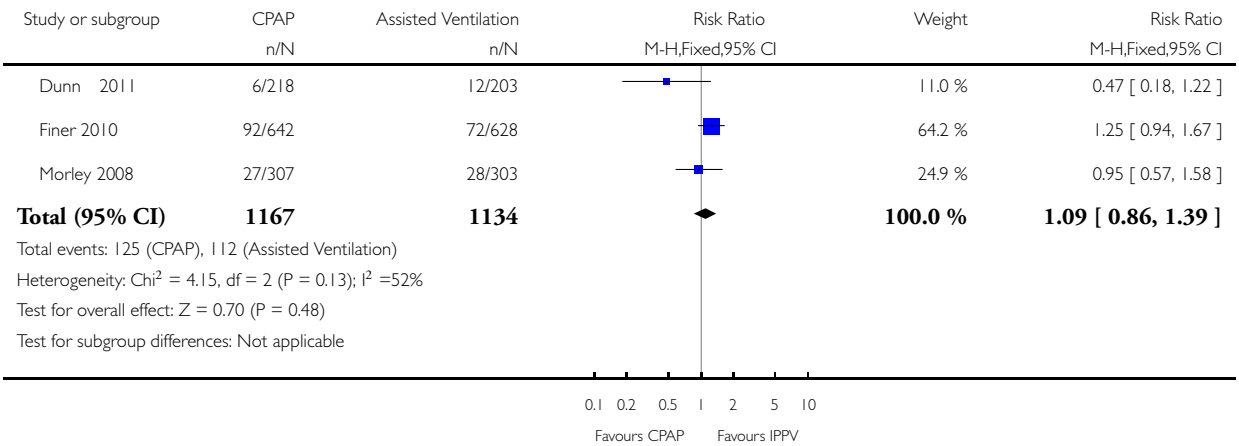



### Analysis 2.12. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 12 IVH grade 3 or 4.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 12 IVH grade 3 or 4





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### Analysis 2.13. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 13 Periventricular leukomalacia.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 13 Periventricular leukomalacia

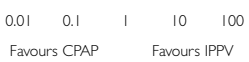
| Study or subgroup | CPAP n/N | Assisted Ventilation n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Dunn 2011 | 3/206 | 2/190 | | 18.6 % | 1.38 [ 0.23, 8.19 ] |
| Morley 2008 | 9/307 | 12/303 | | 81.4 % | 0.74 [ 0.32, 1.73 ] |
| **Total (95% CI)** | **513** | **493** | | **100.0 %** | **0.83 [ 0.39, 1.79 ]** |

Total events: 12 (CPAP), 14 (Assisted Ventilation)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable





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### Analysis 2.14. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 14 Necrotizing enterocolitis.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 14 Necrotizing enterocolitis

| Study or subgroup | CPAP n/N | Assisted Ventilation n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Dunn 2011 | 18/222 | 14/209 | | 15.4 % | 1.21 [ 0.62, 2.37 ] |
| Finer 2010 | 83/654 | 63/636 | | 68.4 % | 1.28 [ 0.94, 1.74 ] |
| Morley 2008 | 12/307 | 15/303 | | 16.2 % | 0.79 [ 0.38, 1.66 ] |
| **Total (95% CI)** | **1183** | **1148** | | **100.0 %** | **1.19 [ 0.92, 1.55 ]** |

Total events: 113 (CPAP), 92 (Assisted Ventilation)

Heterogeneity: $Chi^2$ = 1.39, df = 2 (P = 0.50); $I^2$ =0.0%

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable


### Analysis 2.15. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 15 Sepsis.

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 15 Sepsis

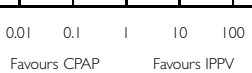
| Study or subgroup | CPAP n/N | Assisted Ventilation n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Dunn 2011 | 17/220 | 27/205 | | 100.0 % | 0.59 [ 0.33, 1.04 ] |
| **Total (95% CI)** | **220** | **205** | | **100.0 %** | **0.59 [ 0.33, 1.04 ]** |

Total events: 17 (CPAP), 27 (Assisted Ventilation)

Heterogeneity: not applicable

Test for overall effect: Z = 1.81 (P = 0.070)

Test for subgroup differences: Not applicable





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**Analysis 2.16. Comparison 2 Prophylactic CPAP vs assisted ventilation, Outcome 16 Retinopathy of prematurity grade 3 or 4.**

Review: Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants

Comparison: 2 Prophylactic CPAP vs assisted ventilation

Outcome: 16 Retinopathy of prematurity grade 3 or 4

| Study or subgroup | CPAP n/N | Assisted Ventilation n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Dunn 2011 | 13/192 | 7/183 | | 9.6 % | 1.77 [ 0.72, 4.34 ] |
| Finer 2010 | 67/511 | 65/473 | | 90.4 % | 0.95 [ 0.69, 1.31 ] |
| **Total (95% CI)** | **703** | **656** | | **100.0 %** | **1.03 [ 0.77, 1.39 ]** |

Total events: 80 (CPAP), 72 (Assisted Ventilation)

Heterogeneity: $Chi^2$ = 1.63, df = 1 (P = 0.20); $I^2$ =39%

Test for overall effect: Z = 0.21 (P = 0.83)

Test for subgroup differences: Not applicable


# APPENDICES

## Appendix 1. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomised controlled trial or controlled clinical trial or randomised or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomised controlled trial OR controlled clinical trial OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)


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Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

## FEEDBACK

### Feedback from C Morley, 21 May 2009

#### Summary

If the review is "Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants", then I think you should include the COIN trial. The other situation where the word prophylactic is used is for surfactant. You can argue about the minutiae of the definition of prophylactic but the COIN trial was the largest RCT so far to enrol infants to nasal CPAP within 5 minutes of birth and therefore it really fulfils the definition of prophylactic.

#### Reply

Feedback Comment:
To be included in COIN, babies had to have some respiratory distress at 5 minutes of age Therefore this is treatment not prophylaxis. This included the subjective and inaccurate sign of cyanosis. The numbers of infants eligible by gestational age but excluded because they had no respiratory distress isn't captured in the paper and I don't think we have the unpublished data to tell. In practice, lack of respiratory distress was a very rare exclusion criteria at RWH where most of the babies were recruited. The spirit of the trial was that babies who were breathing at 5 minutes were randomised but they had signs of respiratory distress and or failure (cyanosis) which I guess makes it not suitable for inclusion in the prophylaxis review rather than the treatment review

#### Contributors

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David J Henderson-Smart
Peter G Davis
Prema Subramaniam

## WHAT'S NEW

Last assessed as up-to-date: 31 January 2016.

| Date | Event | Description |
|---|---|---|
| 16 February 2016 | New citation required and conclusions have changed | In our original comparison, standard care was not defined. We therefore have clarified this by dividing standard care into two groups of comparisons - supportive care and mechanical ventilation allowing us to do away with the term 'standard care' |


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(*Continued*)

| | | |
|---|---|---|
| 16 February 2016 | New search has been performed | This review updates the previous version published in Issue 1, 2009. The background section has been updated and a new search has resulted in the inclusion of five new studies. Another study previously awaiting further assessment has been included in the review but not in the analysis.The methods section has been modified to meet current standards of describing methods without any substantive change in the original methods used. This has lead to a more complete description of assessment of risk of bias, the methods used in the analysis and exploration of heterogeneity. This was done prior to performing the search and analysis |

## HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 4, 1998

| Date | Event | Description |
|---|---|---|
| 12 March 2009 | New search has been performed | This review updates the existing review of 'Prophylactic nasal continuous positive airways pressure to prevent morbidity and mortality in preterm infants' published in The Cochrane Library Issue 3, 2005 (Subramaniam 2005).<br>The updated search included two additional studies One of these studies, the COIN trial (Morley 2008), had previously been referenced as an "Ongoing study" has now been completed |
| 16 October 2008 | Amended | Converted to new review format. |
| 20 April 2005 | New search has been performed | This review updates the existing review of 'Prophylactic nasal continuous positive airways pressure to prevent morbidity and mortality in preterm infants' which was published in The Cochrane Library Issue 2, 2002 (Subramaniam 2002).<br><br>The search revealed one new published eligible trial Sandri (2004). Author clarification regarding randomization and outcome definitions has been received for one trial (Han 1987) and added to the review. The completed trial by Thomson has not been published except in abstract form and is in the 'Trials awaiting assess- |


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(*Continued*)

| | | |
|---|---|---|
| | | ment' section |
| 20 April 2005 | New citation required but conclusions have not changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

PS along with the late DHS (see acknowledgement) developed the protocol; JJH did not participate in the development of the protocol but was involved in post hoc changes to the protocol made in this update. All authors evaluated the studies and extraction of the data.

PS and JJH wrote the text of this update with PGD's input.

The search update was carried out by PS and JJH.

All review authors participated in evaluation of the new trials, data extraction and contributed to updating the review.

## DECLARATIONS OF INTEREST

None

## SOURCES OF SUPPORT


### Internal sources

- Department of Paediatrics, Ipoh Hospital, Ipoh, Malaysia.
- Penang Medical College, Malaysia.
- Royal Women's Hospital, Melbourne, Australia.
- Royal Prince Alfred Hospital, Sydney, Australia.
- Centre for Perinatal Health Services Research, University of Sydney, Australia.

### External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The initial protocol compared prophylactic CPAP with 'standard methods of treatment'. We have since retired the term standard treatment and instead added two comparisons: i.e. comparison 1 is CPAP versus supportive care and comparison 2 is CPAP versus mechanical ventilation.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Positive-Pressure Respiration; Chronic Disease; Infant, Low Birth Weight; Infant, Premature; Infant, Premature, Diseases [mortality; *prevention & control]; Lung Diseases [*prevention & control]; Oxygen Inhalation Therapy; Respiration, Artificial

### MeSH check words

Humans; Infant, Newborn


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