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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 5
OBJECTIVES 6
METHODS 6
RESULTS 8
Figure 1. 9
Figure 2. 11
Figure 3. 12
Figure 4. 13
Figure 5. 14
Figure 6. 15
Figure 7. 16
DISCUSSION 18
AUTHORS' CONCLUSIONS 20
ACKNOWLEDGEMENTS 20
REFERENCES 21
CHARACTERISTICS OF STUDIES 27
DATA AND ANALYSES 44
Analysis 1.1. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 1: Treatment failure 46
Analysis 1.2. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 2: Mortality before discharge 46
Analysis 1.3. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 3: Pneumothorax 47
Analysis 1.4. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 4: Moderate-severe nasal injury 47
Analysis 1.5. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 5: Bronchopulmonary dysplasia 48
Analysis 1.6. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 6: Duration of CPAP use 48
Analysis 1.7. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 7: Duration of oxygen supplementation 49
Analysis 1.8. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 8: Duration of hospitalisation 49
Analysis 1.9. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 9: Patent ductus arteriosus 49
Analysis 1.10. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 10: Necrotising enterocolitis 50
Analysis 1.11. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 11: Severe intraventricular haemorrhage 50
Analysis 1.12. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 12: Severe retinopathy of prematurity 51
APPENDICES 51
CONTRIBUTIONS OF AUTHORS 61
DECLARATIONS OF INTEREST 61
SOURCES OF SUPPORT 61
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 62

[Intervention Review]

Bubble devices versus other pressure sources for nasal continuous positive airway pressure in preterm infants

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ABSTRACT

Background

Several types of pressure sources, including underwater bubble devices, mechanical ventilators, and the Infant Flow Driver, are used for providing continuous positive airway pressure (CPAP) to preterm infants with respiratory distress. It is unclear whether the use of bubble CPAP versus other pressure sources is associated with lower rates of CPAP treatment failure, or mortality and other morbidity.

Objectives

To assess the benefits and harms of bubble CPAP versus other pressure sources (mechanical ventilators or Infant Flow Driver) for reducing treatment failure and associated morbidity and mortality in newborn preterm infants with or at risk of respiratory distress.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 1); MEDLINE (1946 to 6 January 2023), Embase (1974 to 6 January 2023), Maternity & Infant Care Database (1971 to 6 January 2023), and the Cumulative Index to Nursing and Allied Health Literature (1982 to 6 January 2023). We searched clinical trials databases and the reference lists of retrieved articles.

Selection criteria

We included randomised controlled trials comparing bubble CPAP with other pressure sources (mechanical ventilators or Infant Flow Driver) for the delivery of nasal CPAP to preterm infants.

Data collection and analysis

We used standard Cochrane methods. Two review authors separately evaluated trial quality, extracted data, and synthesised effect estimates using risk ratio (RR), risk difference (RD), and mean difference. We used the GRADE approach to assess the certainty of the evidence for effects on treatment failure, all-cause mortality, neurodevelopmental impairment, pneumothorax, moderate-severe nasal trauma, and bronchopulmonary dysplasia.

Main results

We included 15 trials involving a total of 1437 infants. All trials were small (median number of participants 88). The methods used to generate the randomisation sequence and ensure allocation concealment were unclear in about half of the trial reports. Lack of measures to blind caregivers or investigators was a potential source of bias in all of the included trials. The trials took place during the past 25 years

in care facilities internationally, predominantly in India (five trials) and Iran (four trials). The studied pressure sources were commercially available bubble CPAP devices versus a variety of mechanical ventilator (11 trials) or Infant Flow Driver (4 trials) devices.

Meta-analyses suggest that the use of bubble CPAP compared with mechanical ventilator or Infant Flow Driver CPAP may reduce the rate of treatment failure (RR 0.76, 95% confidence interval (CI) 0.60 to 0.95; (I^2 = 31%); RD −0.05, 95% CI −0.10 to −0.01; number needed to treat for an additional beneficial outcome 20, 95% CI 10 to 100; 13 trials, 1230 infants; low certainty evidence). The type of pressure source may not affect mortality prior to hospital discharge (RR 0.93, 95% CI 0.64 to 1.36 (I^2 = 0%); RD −0.01, 95% CI −0.04 to 0.02; 10 trials, 1189 infants; low certainty evidence). No data were available on neurodevelopmental impairment. Meta-analysis suggests that the pressure source may not affect the risk of pneumothorax (RR 0.73, 95% CI 0.40 to 1.34 (I^2 = 0%); RD −0.01, 95% CI −0.03 to 0.01; 14 trials, 1340 infants; low certainty evidence). Bubble CPAP likely increases the risk of moderate-severe nasal injury (RR 2.29, 95% CI 1.37 to 3.82 (I^2 = 17%); RD 0.07, 95% CI 0.03 to 0.11; number needed to treat for an additional harmful outcome 14, 95% CI 9 to 33; 8 trials, 753 infants; moderate certainty evidence). The pressure source may not affect the risk of bronchopulmonary dysplasia (RR 0.76, 95% CI 0.53 to 1.10 (I^2 = 0%); RD −0.04, 95% CI −0.09 to 0.01; 7 trials, 603 infants; low certainty evidence).

Authors' conclusions

Given the low level of certainty about the effects of bubble CPAP versus other pressure sources on the risk of treatment failure and most associated morbidity and mortality for preterm infants, further large, high-quality trials are needed to provide evidence of sufficient validity and applicability to inform context- and setting-relevant policy and practice.

PLAIN LANGUAGE SUMMARY

Pressure sources for nasal continuous positive airway pressure (CPAP) in preterm infants

Key messages

Bubble continuous positive airway pressure (CPAP) may reduce the risk of CPAP treatment failure when compared with CPAP delivered by mechanical ventilators or Infant Flow Driver. Bubble CPAP probably has little or no impact on the risk of death or other complications associated with premature birth but likely increases the risk of moderate-severe nasal injury.

What is CPAP?

CPAP is a form of breathing support that can be used to support breathing in a preterm (premature) baby with lung problems. Various types of machines can provide CPAP, including underwater bubble devices (bubble CPAP), mechanical ventilators, and Infant Flow Driver.

What did we want to find out?

We wanted to determine whether there is evidence to favour bubble systems versus ventilator or Infant Flow Driver systems for reducing the rate of CPAP treatment failure (the baby's condition worsening or the baby needing mechanical ventilation) and reducing complications and harms.

What did we do?

We searched medical databases for randomised controlled trials (a type of study where participants are randomly assigned to one of two or more treatment groups) up to January 2023.

What did we find?

We included 15 trials that compared the use of bubble CPAP versus ventilator or Infant Flow Driver CPAP in a total of 1437 preterm babies. Trials were mostly small, and had design flaws that could put their findings at risk of bias.

Key results

Combined analyses showed that using bubble CPAP rather than ventilator or Infant Flow Driver CPAP may reduce the risk of CPAP treatment failure, but that bubble CPAP may not affect the risk of death or other complications of prematurity. Bubble CPAP likely increases the risk of moderate-severe nasal injury. None of the included studies looked at effects on disability or other developmental outcomes.

What are the limitations of the evidence?

We judged the certainty of the evidence for the effects of bubble versus ventilators or Infant Flow Driver for CPAP in preterm babies to be low because of concerns that the methods used in the included trials may have introduced biases, and the limited amount of data from the trials (meaning the results are less precise). Our confidence in the results is therefore limited.

Summary of findings 1. Bubble versus ventilator or Infant Flow Driver nasal continuous positive airway pressure (CPAP) for preterm infants

Bubble versus ventilator or Infant Flow Driver nasal continuous positive airway pressure (CPAP) in preterm infants

Patient or population: preterm infants receiving nasal CPAP
Setting: neonatal care facilities internationally
Intervention: bubble CPAP
Comparison: ventilator or Infant Flow Driver CPAP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with ventilator or Infant Flow Driver CPAP	Risk with bubble CPAP				
Treatment failure	215 per 1000	163 per 1000 (129 to 204)	RR 0.76 (0.60 to 0.95)	52 per 1000 fewer (11 to 86 fewer per 1000)	1230 (13 studies)	⊕⊕⊙⊙ Low[a,b]
All-cause mortality before hospital discharge	78 per 1000	72 per 1000 (50 to 106)	RR 0.93 (0.64 to 1.36)	6 per 1000 fewer (28 fewer to 28 more per 1000)	1189 (10 studies)	⊕⊕⊙⊙ Low[a,b]
Neurodevelopmental impairment	Not assessed in any included trials					
Pneumothorax	31 per 1000	23 per 1000 (13 to 42)	RR 0.73 (0.40 to 1.34)	8 per 1000 fewer (18 fewer to 11 more per 1000)	1340 (14 studies)	⊕⊕⊙⊙ Low[a,b]
Moderate-severe nasal injury	48 per 1000	109 per 1000 (65 to 182)	RR 2.29 (1.37 to 3.82)	61 per 1000 more (17 to 134 more per 1000)	753 (8 studies)	⊕⊕⊕⊙ Moderate[a]
Bronchopulmonary dysplasia	167 per 1000	127 per 1000 (89 to 184)	RR 0.76 (0.53 to 1.10)	40 per 1000 fewer (78 fewer to 17 more per 1000)	603 (7 studies)	⊕⊕⊙⊙ Low[a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ (relative risk) of the intervention (and its 95% confidence interval)

CI: confidence interval; **CPAP:** continuous positive airway pressure; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded one level for serious study design limitations (high risk of bias due to lack of blinding of clinicians and outcome assessment) in all trials.
[b]Downgraded one level for serious imprecision of effect estimate (95% CI around estimate consistent with substantial harm or benefit).

BACKGROUND

Nasal continuous positive airway pressure (CPAP) is a recommended and widely used method of providing non-invasive respiratory support for spontaneously breathing preterm infants with or at risk of respiratory distress syndrome (Lissauer 2017; Beltempo 2018; Sweet 2019). The most common sources of pressure generation for CPAP are underwater tube 'bubble' systems, mechanical ventilators, and Infant Flow Driver. These pressure sources may differ in their effectiveness of CPAP delivery for several reasons (Green 2019). This review focused on examining whether different sources of pressure generation (bubble CPAP versus ventilator or Infant Flow Driver) affects the risk of treatment failure and associated mortality and morbidity in preterm infants. Other Cochrane Reviews have assessed the effects of different CPAP nasal interfaces and pressure levels in preterm infants (Bamat 2021; De Paoli 2021), and the effects of newer forms of non-invasive ventilation including bilevel positive airway pressure and non-invasive positive pressure ventilation (Lemyre 2016; Lemyre 2017). The use of nasal cannulae for delivering heated and humidified air or supplemental oxygen at high flow rates to generate a distending pressure (but without an intrinsic pressure monitoring or pressure relief/blow-off system) is also the subject of a separate Cochrane Review (Wilkinson 2016).

Description of the condition

Respiratory distress syndrome (RDS) is an important cause of morbidity and mortality in preterm infants (Fraser 2004). RDS is primarily caused by deficiency of alveolar surfactant. As most surfactant is produced after about 32 weeks' gestation, very preterm infants born before then are at high risk of developing RDS. The incidence and severity of RDS increases with decreasing gestational age at birth, occurring in more than 80% of extremely preterm infants born before 28 weeks' gestation (Stoll 2015). If left untreated, the structurally immature and surfactant-deficient lung has a tendency to segmental collapse and atelectasis, ventilation-perfusion mismatch, and pulmonary hypertension that worsens hypoxia and hypercarbia. Consequently, infants with severe RDS can become fatigued and apnoeic and require supplemental oxygen and assisted ventilation (Sweet 2019). Mechanical ventilation via an endotracheal tube, especially if associated with high airway pressures and high concentrations of oxygen, may cause iatrogenic injuries that contribute to the pathogenesis of bronchopulmonary dysplasia (Laughton 2011). Preterm infants who experience severe RDS are at high risk of other morbidities including pneumothorax, persistent patent ductus arteriosus, severe intraventricular haemorrhage, retinopathy of prematurity, and necrotising enterocolitis, that are associated with a prolonged need for respiratory support and hospitalisation, and with mortality and neurodevelopmental impairment (Horbar 2012).

Two major advances in perinatal care - antenatal corticosteroids to stimulate endogenous surfactant production and exogenous surfactant replacement - have greatly improved respiratory and other outcomes for preterm infants, particularly very preterm infants (Curstedt 2015; McGoldrick 2020). Following the widespread adoption of these interventions over the past several decades, the principal form of respiratory support for preterm infants with or at risk of RDS has moved from mechanical ventilation via an endotracheal tube to non-invasive ventilation, most commonly via nasal CPAP devices (Stoll 2015; Soll 2019).

Nasal CPAP maintains low pressure (typically 5 to 8 cm H_2O) distension of the lungs when infants are breathing spontaneously and thereby increases functional residual capacity and improves oxygenation (Wright 2016). Other effects include conserving surfactant and reducing alveolar fluid, dilating the larynx to reduce supraglottic airway resistance, synchronising respiratory thoraco-abdominal movements, and enhancing the Hering-Breuer inflation reflex following airway occlusion (Krouskop 1975; Martin 1977; Yu 1977; Richardson 1978; Miller 1985; Gaon 1999; De Paoli 2005). There is evidence showing that use of nasal CPAP (compared to spontaneous breathing) reduces the risk of respiratory failure, receipt of mechanical ventilation, and mortality in preterm infants with respiratory distress (Ho 2020).

Treatment failure

Nasal CPAP and other modalities of non-invasive respiratory support aim to prevent the iatrogenic problems associated with mechanical ventilation via an endotracheal tube and minimise ventilator-induced lung injury and other complications (Glaser 2021). Evidence from randomised controlled trials suggests that use of nasal CPAP (compared to mechanical ventilation via an endotracheal tube) for primary respiratory support reduces the risk of bronchopulmonary dysplasia in preterm infants and reduces the need for endotracheal re-intubation in preterm infants following a period of mechanical ventilation (Davis 2003; Subramaniam 2016). The effect size of these benefits, however, is limited due to the high rate of CPAP 'treatment failure' - almost half of all very preterm infants treated with nasal CPAP require endotracheal intubation and mechanical ventilation during the first week after birth (Dargaville 2016; Thukral 2016). Treatment failure occurs more commonly in extremely preterm infants, and prolongs the need for respiratory support and supplemental oxygen and is associated with an increased risk of death or bronchopulmonary dysplasia (Dargaville 2013).

Several factors are thought to affect the risk of treatment failure and associated complications in preterm infants, including the CPAP interface (e.g. mask versus prongs) and pressure levels ('low' (~4 to 5 cm H_2O) versus 'high' (~7 to 8 cm H_2O)). These factors are considered in separate Cochrane Reviews (Bamat 2021; De Paoli 2021). This review focused on assessing the trial evidence for the effect of different pressure sources - bubble CPAP versus ventilator or Infant Flow Driver - on treatment failure, and mortality and morbidity in preterm infants.

Description of the intervention

Several sources of pressure generation are available and in use (with considerable variation in practice) (Pillow 2012; Gupta 2016; Mukerji 2017; Ekhaguere 2019):

- underwater (water-seal) 'bubble' CPAP (continuous flow generating an expiratory resistance depending on the depth of submersion underwater of the distal end of the expiratory limb of the circuit);
- mechanical ventilator (continuous flow generating CPAP via expiratory limb resistance or variable-flow CPAP using the Venturi principle to generate pressure at the nasal level via a titratable valve);
- Infant Flow Driver (variable flow CPAP with a constant pressure set at the nasal level using a flow generator attached to device-specific short binasal prongs).

Bubble CPAP has been in use as a means of respiratory support in preterm infants since the early 1970s (Gregory 1971). In addition to commercially manufactured devices (e.g. Fisher & Paykel), less complex bubble CPAP systems can be adapted from modified oxygen cannulae connected to a bubble bottle (Welty 2016; WHO 2016). Such bubble systems are the most widely used form of CPAP in low- and middle-income countries due to their simplicity of design, ease of use, and low cost (Thukral 2016; Won 2019).

Commercially available mechanical ventilator CPAP devices that incorporate flow resistance valves on the expiratory limb of the nasal CPAP circuit are more commonly used in high-income settings. In other ventilator CPAP systems, pressure is generated at the nasal level by a gas-jet device that adjusts the gas flow based on sensed pressure (Kamper 1990).

Infant Flow Driver (Electro Medical Equipment Ltd, Brighton, Sussex, UK; SiPAP System, CareFusion, San Diego, USA), a technologically complex CPAP system used mainly in well-resourced settings, sets a constant distending pressure using a nasal device controlled directly by gas flow (Moa 1993; Moa 1998).

How the intervention might work

The constancy of the delivered distending pressure throughout the respiratory cycle determines the effectiveness of CPAP in optimising alveolar recruitment, functional residual capacity, and (therefore) gas exchange (Pillow 2012). The pressure source (bubble versus ventilator or Infant Flow Driver) is thought to be a key determinant of CPAP stability, although several other factors including the nasal interface (e.g. masks versus prongs) can contribute (De Paoli 2021).

Bubble CPAP, in addition to maintaining a stable end-distending pressure, generates respiratory tract vibrations that improve gas exchange by delivering low-amplitude, high-frequency oscillations at the alveolar level (Lee 1998). Evidence from experimental animal models of RDS suggests that bubble CPAP improves lung recruitment and gas exchange compared with constant-pressure CPAP (Pillow 2007). It has been suggested that the oscillations generated by bubbles in the water column might decrease ventilation-perfusion mismatch similarly to one putative mechanism of action of high-frequency oscillatory ventilators (Gupta 2016; Gupta 2016a). Uncertainty remains, however, regarding how and to what extent the bubbling affects respiratory parameters in preterm infants with RDS (Morley 2005). There is some evidence showing that bubble CPAP may increase the resistive work of breathing and respiratory cycle asynchrony, potentially increasing the risk of treatment failure compared with ventilator CPAP, and that pressure fluctuations can be accentuated to dangerous levels by accumulations of condensate in the expiratory limb of the ventilatory circuit (Liptsen 2005; Youngquist 2013). Furthermore, there is concern that transmission of oscillation and vibration to the bubble CPAP interface may increase the risk of nasal injury and trauma compared with constant-pressure CPAP (Imbulana 2018).

Why it is important to do this review

International policy statements that exist to guide practice do not make unconditional recommendations about which pressure source to use in providing CPAP for preterm infants (Committee on Fetus and Newborn 2014). Given the possibility and plausibility that the choice of pressure source for delivering CPAP may affect the risk of treatment failure and associated mortality and morbidity in preterm infants, appraising and synthesising the trial evidence could inform practice, policy, and research.

OBJECTIVES

To assess the benefits and harms of bubble CPAP versus other pressure sources (mechanical ventilators or Infant Flow Driver) for reducing treatment failure and associated morbidity and mortality in newborn preterm infants with or at risk of respiratory distress.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (including cluster-randomised controlled trials).

Cross-over studies were not eligible for inclusion.

Types of participants

Preterm infants (< 37 weeks' gestation) supported with nasal CPAP, either as primary treatment for respiratory distress after birth, or following a period of mechanical ventilation (postextubation).

Types of interventions

Underwater bubble CPAP devices compared with ventilator or Infant Flow Driver CPAP devices.

Types of outcome measures

We focused on infant- and family-important outcomes, principally CPAP treatment failure and neonatal morbidities that plausibly affect rates of mortality or neurodevelopmental impairment. We did not include surrogate outcomes such as physiological measures of respiratory function.

Primary outcomes

- Treatment failure indicated by recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement, or the receipt of mechanical ventilation within 72 hours after initiation of nasal CPAP
- All-cause mortality prior to hospital discharge
- Neurodevelopmental impairment assessed by a validated test after 12 months' post-term: neurological evaluations, developmental scores, and classifications of disability, including cerebral palsy and auditory and visual impairment

Secondary outcomes

- Pneumothorax (including pneumomediastinum, pneumopericardium) before hospital discharge
- Moderate-severe nasal trauma defined by trial investigators including ulceration, bleeding, septal injury, scarring (not including hyperaemia or erythema)
- Bronchopulmonary dysplasia: oxygen or respiratory support requirement at 36 weeks' postmenstrual age (Jobe 2001; Ehrenkranz 2005)
- Duration of CPAP use (days)
- Duration of oxygen supplementation (days)

- Duration of hospitalisation (days)
- Patent ductus arteriosus receiving medical or surgical treatment
- Necrotising enterocolitis (Bell stage 2 or greater) (Bell 1978)
- Severe intraventricular haemorrhage (Papile 1978)
- Severe retinopathy of prematurity (ICROP 2005)

Search methods for identification of studies

An information specialist developed the search strategies in consultation with the review authors.

Electronic searches

We searched the following databases on 6 January 2023 without language or date restrictions:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 1) in the Cochrane Library (Wiley);
- MEDLINE Ovid (1946 to 6 January 2023);
- Embase Ovid (1974 to 6 January 2023);
- Maternity & Infant Care Database (MIDRIS) Ovid (1971 to 6 January 2023);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to 6 January 2023).

The search strategies combined controlled vocabulary and text words; complete search strategies are shown in Appendix 1, Appendix 2, Appendix 3, Appendix 4, and Appendix 5. Clinical trial filters were used, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Searching other resources

We searched the following clinical trials registries on 6 January 2023 for ongoing or recently completed trials:

- US National Library of Medicine ClinicalTrials.gov (clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform);
- ISRCTN registry (www.isrctn.com/).

Search strategies for the trial registries are shown in Appendix 6.

We searched the reference lists of included studies.

Data collection and analysis

We used the standard methods of Cochrane Neonatal.

Selection of studies

One review author (WM) screened the titles and abstracts of all records identified by the search, coding each record as 'order' or 'exclude'. A second team member (RP) assessed all records coded as 'order' and made the final decision as to which records were retrieved as full-text articles. Two review authors (WM and RP or SO) read the full texts and, using a checklist, assessed the eligibility of each article for inclusion on the basis of prespecified inclusion and exclusion criteria. One review author (ADP) checked these decisions.

Data extraction and management

Two review authors (RP and WM or SO) independently extracted data on design, methods, participants, interventions, outcomes, and treatment effects from each included study using a data collection form to aid extraction. We discussed disagreements until we reached consensus. If data from the trial reports were insufficient, we contacted trialists for further information.

Assessment of risk of bias in included studies

Two review authors (WM and RP or SO) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane risk of bias tool for the following domains (Higgins 2011):

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Any other bias

Any disagreements were resolved by discussion or by consulting a third assessor. For a more detailed description of risk of bias for each domain, see Appendix 7.

Measures of treatment effect

We calculated risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). When we deemed it appropriate to combine two or more study arms, we obtained treatment effects from combined data using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). We determined the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for outcomes with a detected RD.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials. For cluster-randomised trials (had we identified any for inclusion), we planned to undertake analyses at the level of the individual whilst accounting for clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Dealing with missing data

We requested additional data from trial investigators when data on important outcomes were missing or were reported unclearly. When data remained missing, we planned to examine the impact on effect size estimates by performing sensitivity analyses.

Assessment of heterogeneity

We examined treatment effects in individual trials and heterogeneity between trial results by inspecting forest plots if more than one trial was included in a meta-analysis. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate or high (I^2 >

50%) levels of heterogeneity, we explored possible causes by performing prespecified subgroup analyses (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We assessed reporting bias by comparing the stated primary outcomes and secondary outcomes and the reported outcomes. Where study protocols were available, we compared these to the full publications to determine the likelihood of reporting bias. Studies using the interventions in a potentially eligible infant population but not reporting on any of the primary and secondary outcomes of this review were documented in Characteristics of included studies. We planned to use funnel plots to screen for publication bias where there was a sufficient number of trials (at least 10) reporting the outcome. If publication bias was suggested by asymmetry of the funnel plot on visual assessment, we planned to assess this statistically use Harbord's modification of Egger's test (Harbord 2006).

Data synthesis

We used a fixed-effect model inverse variance meta-analysis for combining data where trials examined the same intervention and the populations and methods of the trials were judged to be similar.

Subgroup analysis and investigation of heterogeneity

We prespecified subgroup analyses of bubble CPAP versus:

- ventilator CPAP;
- Infant Flow Driver CPAP.

We planned to explore moderate or high heterogeneity ($I^2 > 50\%$) in subgroup analyses stratified by:

- timing of nasal CPAP: primary support after birth versus postextubation;
- CPAP levels: 'low' (~4 to 5 cm H_2O) versus 'higher' (> 5 cm H_2O);
- gestation or birthweight: preterm or low birthweight versus very preterm or very low birthweight;
- setting: low- or middle-income versus high-income countries (World Bank 2021).

Sensitivity analysis

We planned to perform sensitivity analyses if:

- there was unexplained moderate or high heterogeneity ($I^2 > 50\%$) by removing the outlying trial or trials;
- a trial with high risk of bias (including high level of missing outcome data) was included in the meta-analysis of an outcome where the other studies were at low risk of bias (removing the study with high risk of bias).

Summary of findings and assessment of the certainty of the evidence

Two review authors (SO and WM) used the GRADE approach as outlined in the GRADE Handbook to assess the certainty of the evidence for the following outcomes (Schünemann 2013).

- Treatment failure
- All-cause mortality prior to hospital discharge
- Neurodevelopmental impairment
- Moderate-severe nasal injury
- Pneumothorax
- Bronchopulmonary dysplasia

We considered evidence from randomised controlled trials to be of high certainty, and downgraded one level for serious (or two levels for very serious) limitations based upon: design (risk of bias); consistency across trials; directness of the evidence; precision of estimates; and presence of publication bias (Schünemann 2013; Walsh 2021). We used GRADEpro GDT software to create a summary of findings table to report the certainty of the evidence (GRADEpro GDT).

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades, as follows.

- **High:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **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.
- **Low:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **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.

RESULTS

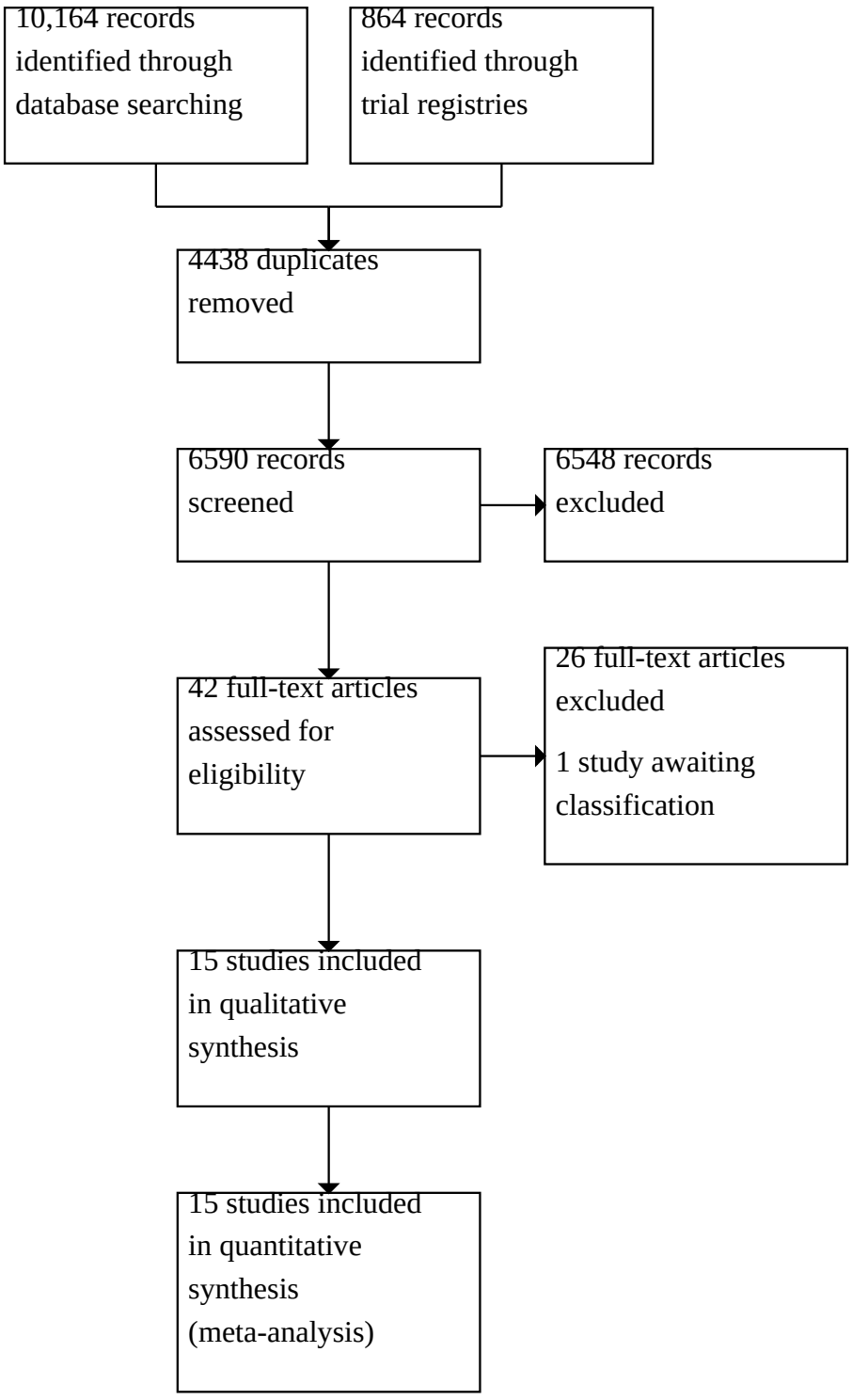
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Our database searches identified 10,164 references, and our searches of the trial registries identified 864 records. After removal of 4438 duplicates, 6590 records were available for screening, of which 6548 were excluded based on title/abstract review. We assessed 42 full-texts, excluding 26 reports (Characteristics of excluded studies). We included 15 studies (Characteristics of included studies) in the quantitative synthesis. We classified one conference abstract as awaiting classification (Characteristics of studies awaiting classification). Details are provided in Figure 1.

Figure 1. Study flow diagram.



Included studies

We included 15 trials involving a total of 1437 infants (Characteristics of included studies). Most trials were small (median number of participants 88). The trials were conducted during the past 25 years in neonatal centres in India (5 trials), Iran (4 trials), Brazil (2 trials), Albania (1 trial), Armenia (1 trial), the UK (1 trial), and Italy (1 trial). Individual infants were allocated randomly to intervention or control groups in all of the trials. No studies used a cluster-randomised design.

All trials used a commercially available bubble CPAP device; none used a low-cost, locally adapted form of bubble CPAP.

Eleven trials compared bubble CPAP with ventilator CPAP (Tagare 2010; Bahman-Bijari 2011; Mohammadizadeh 2011; Yagui 2011; Hosseini 2012; Yadav 2012; Tagare 2013; Bhatti 2015; Agarwal 2016; Noori Shadkam 2017; Ribeiro 2017). Four trials compared bubble CPAP with Infant Flow Driver CPAP (Mazzella 2001; Gupta 2009; Jazexhiu-Postoli 2015; Mazmanyan 2016).

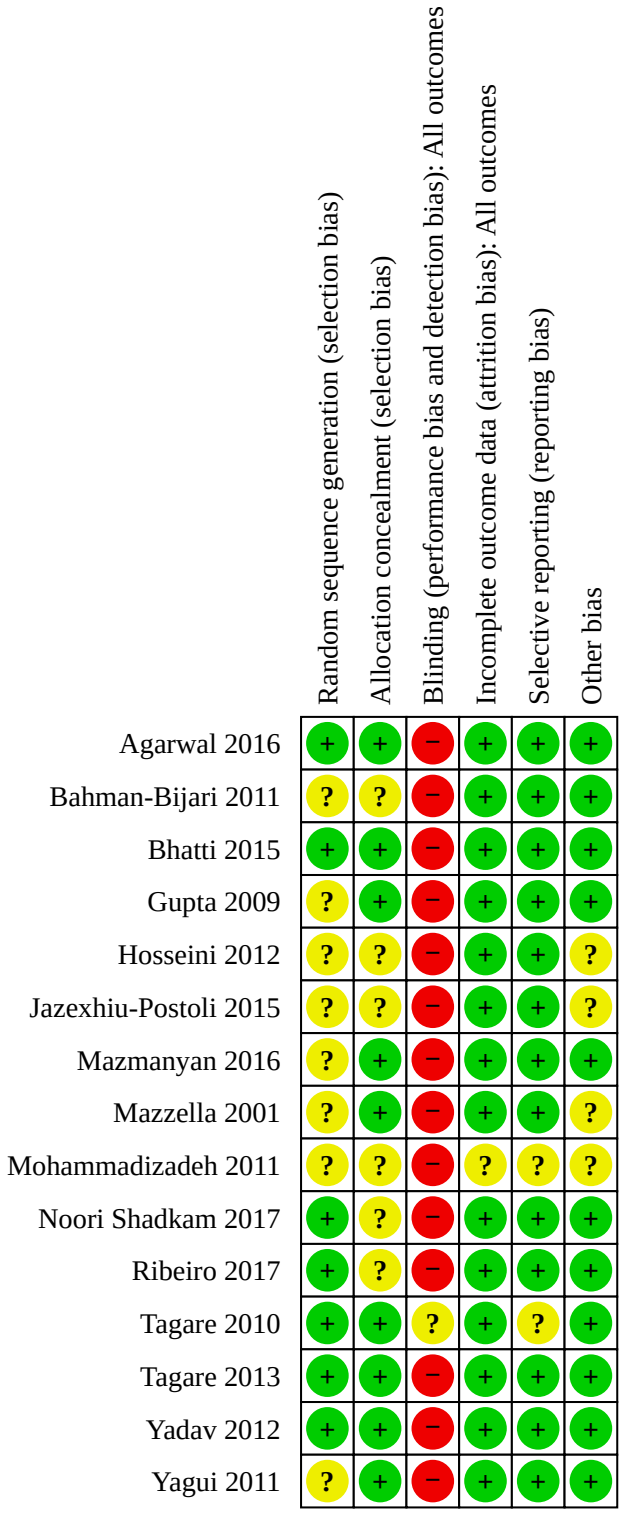
Excluded studies

We excluded 26 reports (Characteristics of excluded studies). The most common reasons for exclusion were wrong study design (non-randomised or cross-over) or wrong intervention (did not include bubble CPAP as a comparison group).

Risk of bias in included studies

Methodologic quality varied between the trials (Figure 2). All trials had unclear or high risk of bias in at least one domain.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The methods used to generate the random sequence and conceal allocation were not described in about half of the trials. The other trials used computer or web-based programs to generate the random sequence and sealed, opaque envelopes to conceal allocation.

Blinding

All trials were 'open-label' - none blinded parents, clinicians, or investigators.

Incomplete outcome data

Most trials reported complete or near-complete assessments of primary outcomes. We assessed one trial as at unclear risk of attrition bias.

Selective reporting

Most trials reported a comprehensive group of infant-important outcomes. We assessed two trials as at unclear risk of reporting bias as they reported few clinical outcomes.

Other potential sources of bias

We did not find evidence of between-group baseline differences in participant characteristics or demographics in most of the trials. Gestation and weight at birth differed between groups in two trials, and baseline characteristics were not presented in two trials (unclear risk).

Effects of interventions

See: **Summary of findings 1** Bubble versus ventilator or Infant Flow Driver nasal continuous positive airway pressure (CPAP) for preterm infants

Primary outcomes

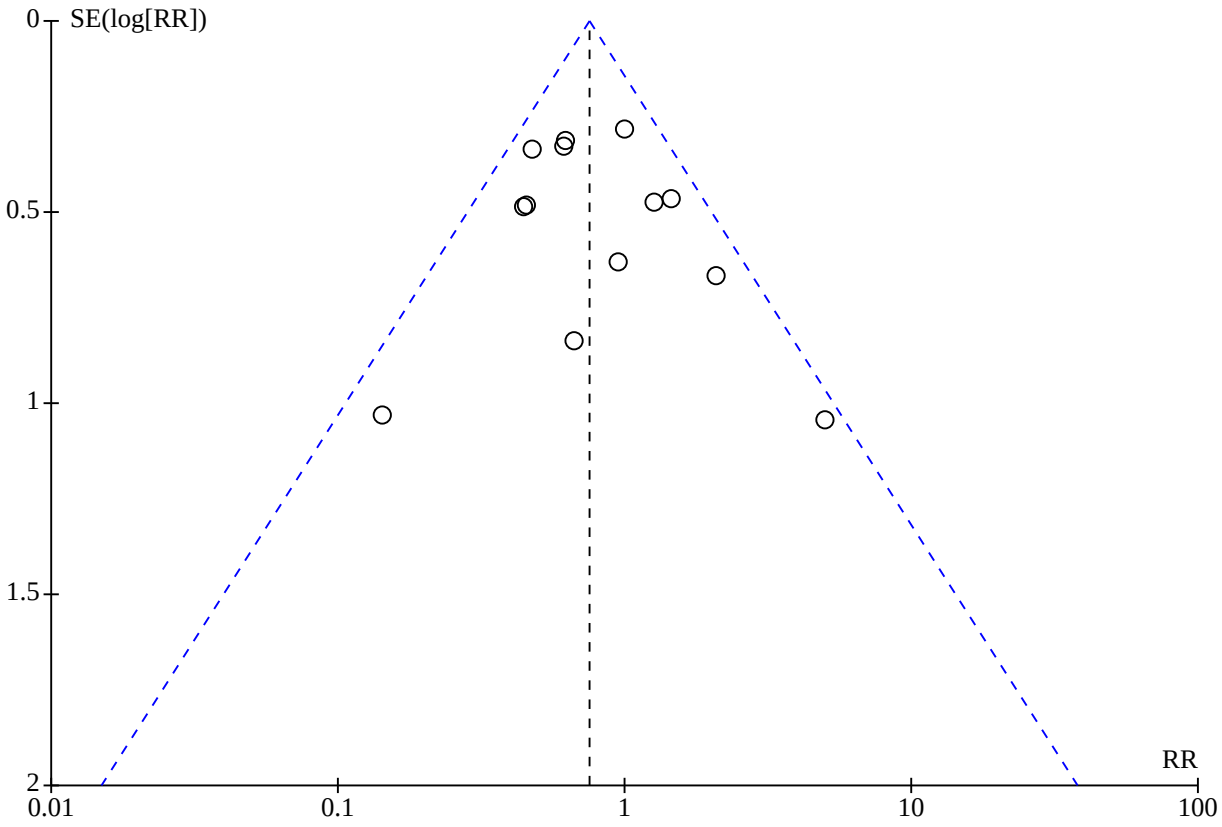
Treatment (CPAP) failure

Meta-analysis of data from 13 trials (1230 infants) suggests that bubble (versus ventilator/Infant Flow Driver) CPAP may reduce the risk of treatment failure slightly (Analysis 1.1):

- risk ratio (RR) 0.76, 95% confidence interval (CI) 0.60 to 0.95 (I^2 = 31%);
- risk difference (RD) −0.05, 95% CI −0.10 to −0.01;
- number needed to treat for an additional beneficial outcome (NNTB) 20, 95% CI 10 to 100.

There was no evidence of funnel plot asymmetry sufficient to suggest publication bias (Figure 3).

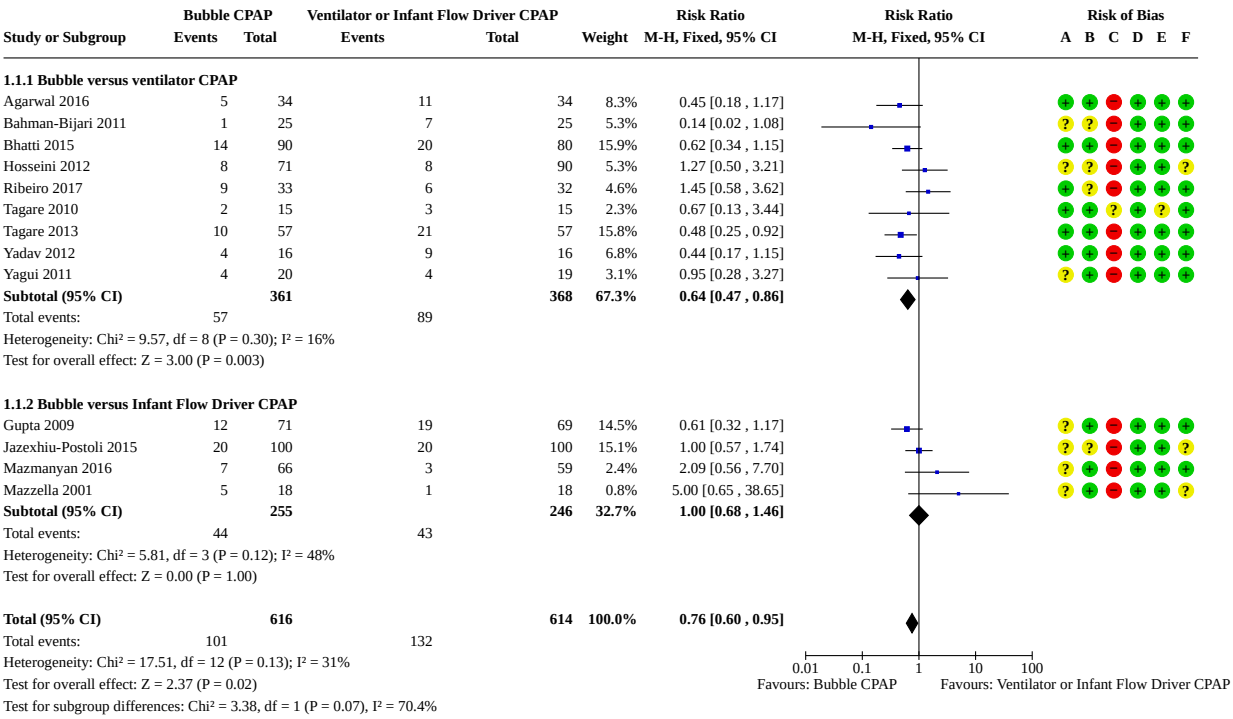
Figure 3. Forest plot of comparison: 1 Bubble CPAP versus ventilator or Infant Flow Driver CPAP, outcome: 1.1 Treatment failure.



We assessed the certainty of evidence as low, downgrading one level for serious study design limitations (lack of blinding) and one level for imprecision (Summary of findings 1).

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: $Chi^2 = 3.38$, df = 1 (P = 0.07), $I^2 = 70.4\%$ (Figure 4).

Figure 4.



Subgroup analysis for heterogeneity

Not applicable ($I^2 = 31\%$).

Sensitivity analysis for heterogeneity

Not applicable ($I^2 = 31\%$).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

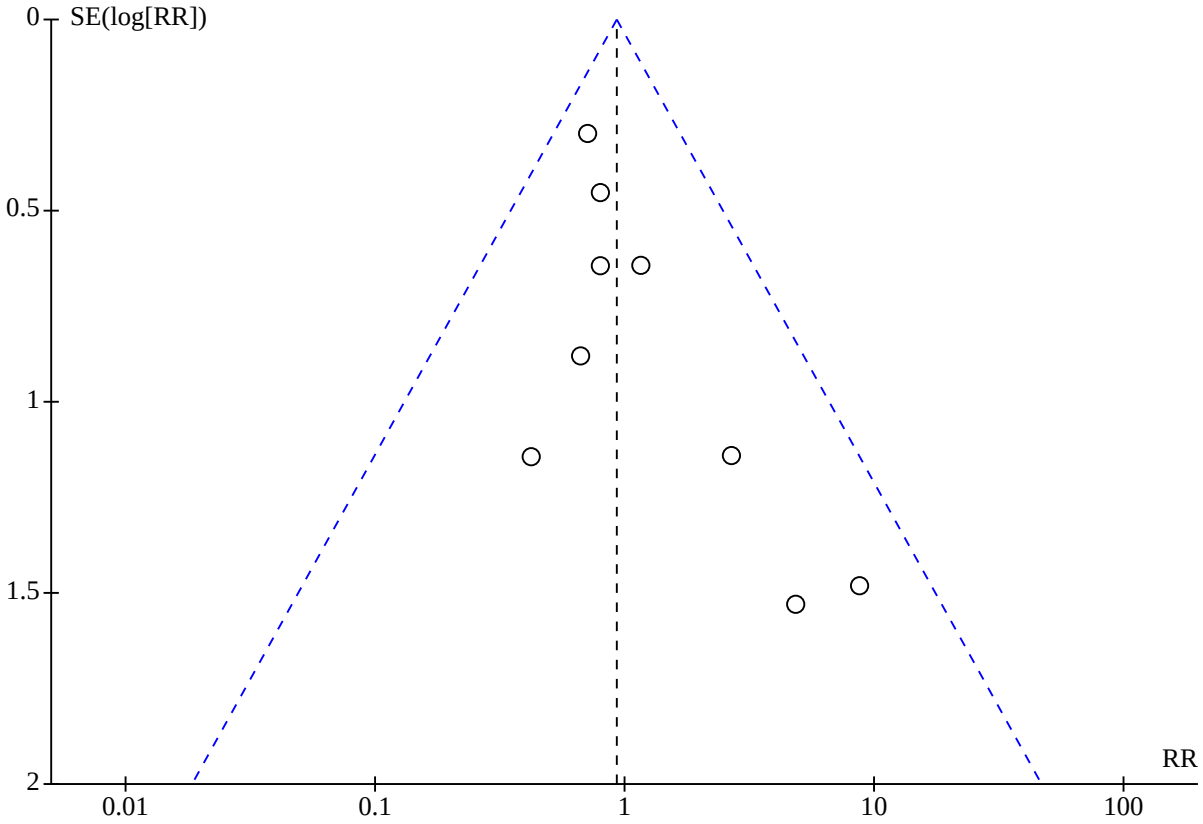
All-cause mortality prior to hospital discharge

Meta-analysis of data from 10 trials (1189 infants) suggests that bubble (versus ventilator/Infant Flow Driver) CPAP may not affect the risk of mortality prior to hospital discharge (Analysis 1.2):

- RR 0.93, 95% CI 0.64 to 1.36 ($I^2 = 0\%$);
- RD −0.01, 95% CI −0.04 to 0.02.

There was no evidence of funnel plot asymmetry sufficient to suggest publication bias (Figure 5).

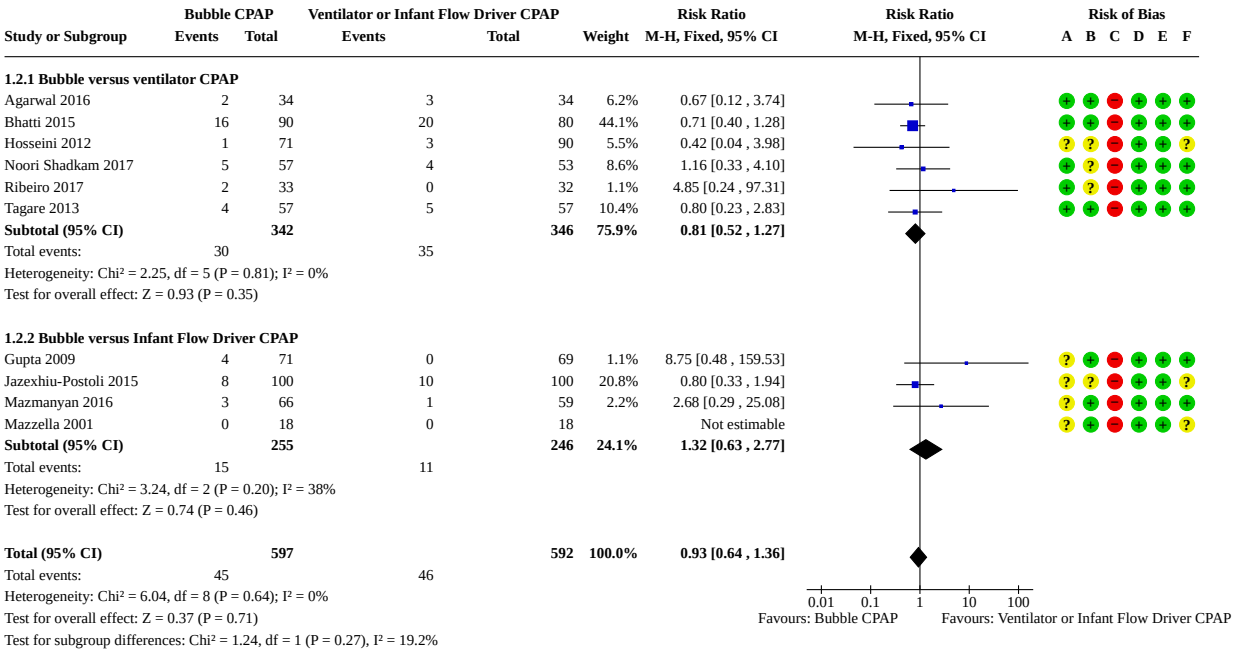
Figure 5. Forest plot of comparison: 1 Bubble CPAP versus ventilator or Infant Flow Driver CPAP, outcome: 1.2 Mortality before discharge.



We assessed the certainty of evidence as low, downgrading one level for serious study design limitations (lack of blinding) and one level for imprecision (Summary of findings 1).

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: $Chi^2 = 1.24$, df = 1 (P = 0.27), $I^2 = 19.2\%$ (Figure 6).

Figure 6.



Subgroup analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Moderate-severe neurodevelopmental impairment

None of the trials assessed neurodevelopmental outcomes.

Secondary outcomes

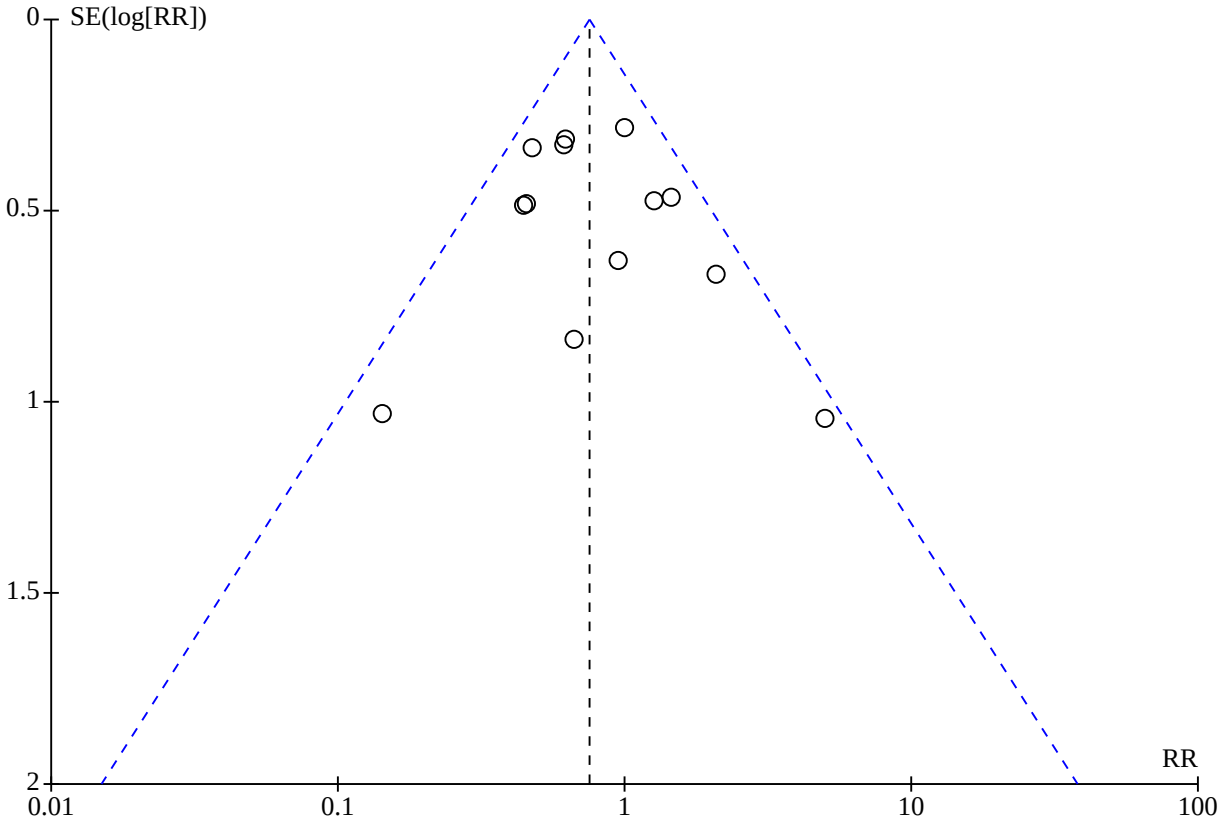
Pneumothorax

Meta-analysis of data from 14 trials (1340 infants) suggests that bubble (versus ventilator/Infant Flow Driver) CPAP may not affect the risk of pneumothorax (Analysis 1.3):

- RR 0.73, 95% CI 0.40 to 1.34 (I^2 = 0%);
- RD −0.01, 95% CI −0.03 to 0.01.

There was no evidence of funnel plot asymmetry sufficient to suggest publication bias (Figure 7).

Figure 7. Forest plot of comparison: 1 Bubble CPAP versus ventilator or Infant Flow Driver CPAP, outcome: 1.3 Pneumothorax.



We assessed the certainty of evidence as low, downgrading one level for serious study design limitations (lack of blinding) and one level for imprecision (Summary of findings 1).

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: $Chi^2 = 1.00$, df = 1 (P = 0.32), $I^2 = 0\%$.

Subgroup analysis for heterogeneity

Not applicable ($I^2 = 0\%$).

Sensitivity analysis for heterogeneity

Not applicable ($I^2 = 0\%$).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Moderate-severe nasal injury

Meta-analysis of data from 8 trials (753 infants) shows that bubble (versus ventilator/Infant Flow Driver) CPAP likely increases the risk of moderate-severe nasal injury slightly (Analysis 1.4):

- RR 2.29, 95% CI 1.37 to 3.82) ($I^2 = 17\%$);
- RD 0.07, 95% CI 0.03 to 0.11;
- number needed to treat for an additional harmful outcome (NNTH) 14, 95% CI 9 to 33.

There were insufficient data points to assess funnel plot asymmetry.

We assessed the certainty of evidence as moderate, downgrading one level for serious study design limitations (lack of blinding) (Summary of findings 1).

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: $Chi^2 = 1.68$, df = 1 (P = 0.19), $I^2 = 40.5\%$.

Subgroup analysis for heterogeneity

Not applicable ($I^2 = 17\%$).

Sensitivity analysis for heterogeneity

Not applicable ($I^2 = 17\%$).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Bronchopulmonary dysplasia

Meta-analysis of data from seven trials (603 infants) suggests that bubble (versus ventilator/Infant Flow Driver) CPAP may not affect the risk of bronchopulmonary dysplasia (Analysis 1.5):

- RR 0.76, 95% CI 0.53 to 1.10 ($I^2 = 0\%$);

- RD −0.04, 95% CI −0.09 to 0.01.

There were insufficient data points to assess funnel plot asymmetry.

We assessed the certainty of evidence as low, downgrading one level for serious study design limitations (lack of blinding), and one level for imprecision (Summary of findings 1).

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: $Chi^2 = 0.46$, df = 1 (P = 0.50), $I^2 = 0\%$.

Subgroup analysis for heterogeneity

Not applicable ($I^2 = 0\%$).

Sensitivity analysis for heterogeneity

Not applicable ($I^2 = 0\%$).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Duration of CPAP use

Meta-analysis of data from eight trials (744 infants) that reported mean and standard deviation (SD) for each group (bubble versus ventilator/Infant Flow Driver) suggests little or no effect:

- mean difference (MD) −0.01, 95% CI −0.16 to 0.13 days ($I^2 = 67\%$) (Analysis 1.6).

There were insufficient data points to assess funnel plot asymmetry.

There was evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: $Chi^2 = 4.81$, df = 1 (P = 0.03), $I^2 = 79.2\%$ (larger effect for bubble CPAP versus Infant Flow Driver CPAP than for bubble CPAP versus ventilator CPAP).

Subgroup analysis for heterogeneity

- CPAP levels: 'low' (up to 5 cm H_2O) versus 'higher' (> 5 cm H_2O): subgroup analysis not feasible, as trials described a range of CPAP levels that typically included both of these ranges.
- Gestation or birthweight: preterm or low birthweight versus very preterm or very low birthweight: subgroup analysis not feasible, as trials described a range of gestational age or birthweight that typically included both of these ranges.
- Setting: low- and middle-income versus high-income countries (World Bank 2021): seven trials took place in low- or middle-income countries (Albania, India, Iran), whilst one trial took place in a high-income country (Italy). There was no evidence of a subgroup effect ($Chi^2 = 0.59$, df = 1 (P = 0.44), $I^2 = 0\%$).

Sensitivity analysis for heterogeneity

Removal of the outlying trial, Jazexhiu-Postoli 2015, reduced the level of heterogeneity. Meta-analysis of the seven remaining trials suggests that bubble (versus ventilator/Infant Flow Driver) CPAP may have little or no effect:

- MD 0.05, 95% CI −0.11 to 0.20 days ($I^2 = 39\%$).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Six trials reported median difference in duration of CPAP use (bubble versus ventilator/Infant Flow Driver), as follows.

Primary support:

- Bhatti 2015: 0.9 days
- Mazmanyan 2016: 0.2 days
- Tagare 2013: 0.2 days
- Yagui 2011: 0.0 days

Postextubation support:

- Gupta 2009: −2.0 days
- Ribeiro 2017: 0.0 days

One trial did not report duration of CPAP use (Yadav 2012).

Duration of oxygen supplementation

Analysis of data from one trial (88 infants) that reported mean and SD for each group (bubble versus ventilator CPAP) suggests little or no effect (Mohammadizadeh 2011):

- MD 0.60, 95% CI −2.52 to 3.72 (Analysis 1.7).

One trial did not show a difference in the median duration of oxygen supplementation with bubble versus ventilator/Infant Flow Driver CPAP as postextubation support (Ribeiro 2017).

The other 13 trials did not report duration of oxygen supplementation.

Duration of hospitalisation

Meta-analysis of data from five trials (591 infants) that reported mean and SD for each group suggests that bubble (versus ventilator/Infant Flow Driver) CPAP may reduce the duration of hospitalisation:

- MD −3.27, 95% CI −4.99 to −1.56 days ($I^2 = 32\%$) (Analysis 1.8).

There were insufficient data points to assess funnel plot asymmetry.

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: $Chi^2 = 2.36$, df = 1 (P = 0.12), $I^2 = 57.7\%$.

Subgroup analysis for heterogeneity

Not applicable ($I^2 = 32\%$).

Sensitivity analysis for heterogeneity

Not applicable ($I^2 = 32\%$).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Two trials did not show a difference in the median duration of hospitalisation with bubble versus ventilator/Infant Flow Driver CPAP, as follows.

- Yagui 2011: −1.5 days
- Ribeiro 2017: −1.0 days

The other eight trials did not report duration of hospitalisation.

Patent ductus arteriosus

Meta-analysis of data from six trials (597 infants) suggests little or no effect of bubble versus ventilator/Infant Flow Driver CPAP (Analysis 1.9):

- RR 0.96, 95% CI 0.67 to 1.38 (I^2 = 0%);
- RD −0.01, 95% CI −0.06 to 0.05.

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: Chi^2 = 0.60, df = 1 (P = 0.44), I^2 = 0%.

Subgroup analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Necrotising enterocolitis

Meta-analysis of data from six trials (693 infants) suggests little or no effect of bubble versus ventilator/Infant Flow Driver CPAP (Analysis 1.10):

- RR 0.75, 95% CI 0.39 to 1.44 (I^2 = 0%);
- RD −0.01, 95% CI −0.05 to 0.02.

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: Chi^2 = 0.74, df = 1 (P = 0.39), I^2 = 0%.

Subgroup analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Severe intraventricular haemorrhage

Meta-analysis of data from six trials (562 infants) suggests little or no effect of bubble versus ventilator/Infant Flow Driver CPAP (Analysis 1.11):

- RR 0.81, 95% CI 0.42 to 1.58 (I^2 = 0%);
- RD −0.01, 95% CI −0.05 to 0.03.

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: Chi^2 = 2.01, df = 1 (P = 0.16), I^2 = 50.2%.

Subgroup analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

Severe retinopathy of prematurity

Meta-analysis of data from six trials (642 infants) suggests little or no effect of bubble versus ventilator/Infant Flow Driver CPAP (Analysis 1.12):

- RR 0.92, 95% CI 0.54 to 1.57 (I^2 = 0%);
- RD −0.01, 95% CI −0.05 to 0.03.

There was no evidence of a subgroup difference for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP: Chi^2 = 0.08, df = 1 (P = 0.77), I^2 = 0%.

Subgroup analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for heterogeneity

Not applicable (I^2 = 0%).

Sensitivity analysis for risk of bias

The meta-analysis did not contain data from a trial with high risk of bias where the other studies had low risk of bias.

DISCUSSION

Summary of main results

This review of 15 trials, with 1437 participants in total, suggests that use of bubble compared with ventilator or Infant Flow Driver devices as the pressure source for nasal CPAP in preterm infants may reduce the rate of treatment failure by about one-quarter. The point estimate indicates that, for every 1000 infants treated with bubble CPAP compared with ventilator or Infant Flow Driver devices, there will be 50 fewer episodes of treatment failure.

The available data suggest that the type of pressure source may not affect mortality prior to hospital discharge or the risk of pneumothorax or bronchopulmonary dysplasia. None of the included trials reported the effect on neurodevelopmental impairment. Meta-analysis suggests that bubble CPAP likely increases the risk of moderate-severe nasal injury. Bubble CPAP may be associated with reduced duration of hospitalisation of about three days. Other outcomes such as major morbidities (patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage, retinopathy of prematurity) and duration of CPAP or supplemental oxygen use appear not to be influenced by type of pressure source. However, the numbers of participants and trials to date are low, and the estimates of effect imprecise.

Overall completeness and applicability of evidence

Most of the trials were undertaken within the past 25 years in healthcare facilities internationally, predominantly in middle-income countries (9 of 15 trials occurred in India or Iran). No trials were conducted in sub-Saharan Africa. Most participants were very preterm infants; few were extremely preterm or extremely low birthweight.

The mechanism whereby bubble CPAP may reduce the rate of treatment failure is unclear. Bubble CPAP generates oscillatory waves that may transmit more effectively the prescribed pressure to the airway and alveoli than does constant-pressure CPAP. However, it remains unclear whether or how this physiological phenomenon affects important respiratory parameters in preterm infants (Liptsen 2005). Nevertheless, there were between-trial differences in the definition of CPAP treatment failure (including a broad range of fraction of inspired oxygen (FiO_2) thresholds) that limit the generalisability of the findings. Similarly, although transmission of oscillations and vibration is one putative mechanism by which bubble versus ventilator or Infant Flow Driver CPAP may increase the risk of moderate-severe nasal injury, this effect may be due in part to the confounding influence of different types of nasal interfaces used with the different CPAP pressure sources (De Paoli 2021).

Relevance to resource-limited settings

Various CPAP devices were studied across the included trials, and the findings appear broadly applicable to current care practices for preterm infants receiving bubble or ventilator or Infant Flow Driver CPAP. Prespecified analyses did not show evidence of different subgroup effects for bubble CPAP versus ventilator CPAP compared with bubble CPAP versus Infant Flow Driver CPAP.

However, a major limitation to the applicability of these findings to resource-limited settings is that the bubble CPAP system used in most of the trials was a commercially manufactured device (mostly Fisher & Paykel). Such devices are not affordable in many resource-limited settings in low- or middle-income countries, and low-cost, locally manufactured or locally adapted devices are more commonly used (WHO 2016). These 'indigenous' systems, based on the original bubble CPAP device, consist of a wide-bore inspiratory limb with a low-resistance interface to generate stable positive end-expiratory pressure dependent on the depth of submersion of the expiratory tubing (Baldursdottir 2020). There is some concern that these systems deliver CPAP variably depending on respiratory tubing and flow rates employed (Ettinger 2021). However, none of the included trials compared the effect of these low-cost systems with ventilator or Infant Flow Driver CPAP.

Consequently, this review does not address concerns about the benefits and harms of low-cost, locally manufactured or locally adapted bubble CPAP systems in resource-limited settings. These concerns include uncertainty about the effect of instability in airway pressure due to condensate in the expiratory limb of the respiratory circuit. Since low-cost bubble CPAP systems typically lack pressure alarms and pressure-release valves, potentially harmful high levels of positive end-expiratory pressure may be undetected (Youngquist 2013). Another major concern in some settings is that locally adapted bubble CPAP systems can provide only pure (100%) oxygen due to unavailability of oxygen-air blenders. As a result, if not monitored, infants may be exposed to hyperoxia that may contribute to the epidemic of retinopathy of prematurity in many low- or middle-income countries (Vinekar 2019).

Quality of the evidence

We used GRADE methods to assess the certainty of the evidence for effects on treatment failure, all-cause mortality prior to hospital discharge, neurodevelopmental impairment (no data), pneumothorax, moderate-severe nasal injury, and bronchopulmonary dysplasia (Summary of findings 1). Using this framework, we downgraded the certainty of the evidence from high to low because of methodological weaknesses (risk of bias), in particular uncertainty about the methods used to generate the random sequence and to conceal treatment allocation in about half of the trials, and lack of blinding measures for parents, caregivers, and clinical assessors in all the trials. The methodological weaknesses may have introduced selection, performance, and detection biases. For example, it is possible that bias in the (unrecorded) use of co-interventions such as methylxanthines may have differed between treatment groups, or that surveillance and detection bias for subjective outcomes was introduced (e.g. in checking for nasal injury more often in infants allocated to one pressure source or CPAP device versus another).

The other reason for downgrading the certainty of evidence across all outcomes was the existence of substantial imprecision in the estimates of effect. Meta-analyses generated 95% CI that included large benefit as well as small or no benefit or harm. Although the total number of participants in the 15 included trials was more than 1400, not all trials contributed data to all outcome estimates, and as a result estimates of effect were imprecise, especially for less common outcomes, including mortality. For example, the point estimate for the NNTB for treatment failure was 20, but the upper bound of the 95% CI included an NNTB of 100. Such imprecise estimates of effect are unlikely to meaningfully inform decision-making in this context.

Heterogeneity was not an apparent limitation in the meta-analyses, and planned subgroup analyses to investigate sources of moderate or high heterogeneity (I^2 > 50%) in primary outcomes were not conducted. The absence of such levels of heterogeneity in the meta-analyses may be related to similarity of the trial settings and populations studied, and although a variety of different pressure sources (several types of mechanical ventilator) were used, these are likely to be broadly similar in their mechanisms of action and physiological effects.

Potential biases in the review process

An important concern with the review process is the possibility that the findings are subject to publication and other reporting biases (Hopewell 2009). Data from trials which show statistically significant or potentially important effects tend to be more readily available for inclusion in meta-analyses (Gale 2020). Publication bias, as well as other sources of small-study bias, is an important contributor to inflation of effect size estimates in meta-analyses of interventions to improve outcomes in preterm infants (Walsh 2021).

We did not show funnel plot asymmetry suggesting that publication bias (or other types of small-study biases) exaggerated the effect size in any of the meta-analyses that contained sufficient data points (Higgins 2020). Although we attempted to minimise the

threat of publication bias by screening the reference lists of included trials and related reviews, and searching the proceedings of the major international perinatal conferences to identify trial reports that were not published in full form in academic journals, we cannot be sure that other trials have been undertaken but not reported.

Agreements and disagreements with other studies or reviews

This review is in broad agreement with another recent systematic review of randomised controlled trials that assessed the effects of bubble versus other pressure sources for delivering CPAP for preterm infants (Bharadwaj 2020). Similar to our findings, Bharadwaj 2020 showed that bubble CPAP was associated with a reduced risk of CPAP failure (within seven days). There does not appear to be an effect on mortality or bronchopulmonary dysplasia, but there may be an increase in the risk of nasal injury.

AUTHORS' CONCLUSIONS

Implications for practice

Given the low certainty of the evidence provided by these analyses, the implications for practice remain uncertain. Although the available trial data do suggest that use of bubble CPAP may reduce the risk of treatment failure compared with ventilator or Infant Flow Driver CPAP, because of design limitations (risk of bias) and the paucity of data that could be abstracted from published reports (imprecision), it remains unclear how or if this translates to effects on other important outcomes including mortality, neurodevelopmental impairment, and other major morbidities including bronchopulmonary dysplasia.

Implications for research

Well-designed trials evaluating this important aspect of a recommended and commonly used neonatal therapy are needed. Trials reporting infant-important endpoints such as the primary outcomes of this review will facilitate updating of evidence syntheses. Although blinding of clinical investigators to treatment allocation is likely to be impractical, trials should aim to minimise performance or detection bias, for example by strict and consistent application of protocols for management and criteria for subjective diagnoses such as treatment failure.

In high-income countries with well-resourced healthcare facilities, evaluating the comparative effects of different pressure source devices for CPAP may be particularly relevant to extremely preterm or extremely low birthweight infants at high risk of treatment failure and associated complications including bronchopulmonary dysplasia. However, in these settings research priorities may already have shifted towards comparative studies with the newer forms of non-invasive ventilation (including nasal intermittent positive pressure ventilation and humidified high-flow nasal cannulae) that are increasingly being adopted in practice (Mukerji 2017). These devices are considered in separate Cochrane Reviews (Wilkinson 2016; Lemyre 2017). Furthermore, the clinical and research context for non-invasive ventilation, particularly in well-resourced facilities, has been affected by other innovations including the early use of 'less-invasive surfactant therapy', which is associated with reduced risk of death or bronchopulmonary dysplasia compared with surfactant therapy via an endotracheal tube and continued mechanical ventilation (Abdel-Latif 2021).

In low-income countries with fewer and scarcer healthcare resources, the infant population most likely to be affected are more mature preterm infants in whom CPAP may be life-saving in the absence of intensive care and additional therapies including surfactant and mechanical ventilation (Kinshella 2020). Furthermore, in these settings the bubble CPAP devices of most interest are low-cost, locally manufactured or locally adapted devices rather than commercially manufactured, technologically complex bubble CPAP machines (WHO 2016; Won 2019). However, the feasibility and ethical propriety of conducting trials comparing the use of low-cost bubble CPAP to the best available care practices (including low-flow oxygen without CPAP) is a matter of debate (Ekhaguere 2019).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agarwal 2016

Study characteristics	
Methods	RCT
Participants	68 newborn VLBW infants with moderate respiratory distress (Silverman score 4 to 7) treated with CPAP 5 to 7 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 34 Ventilator (Newport): N = 34 Various nasal CPAP prongs (Argyle, Hudson Binasal or Fisher & Paykel) were used.
Outcomes	CPAP failure (persistent hypoxia with FiO_2 > 0.6 or requiring mechanical ventilation) Death before discharge Receipt of surfactant Duration of CPAP use Pneumothorax Nasal trauma (septal necrosis)
Notes	Setting: Delhi, India (2009 to 2011) Funding: no specific funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed, and stapled envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label

Agarwal 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Bahman-Bijari 2011

Study characteristics	
Methods	RCT
Participants	50 preterm neonates (birthweight 1000 to 2000 g) with respiratory distress (Silverman score 6 to 7) treated with CPAP 5 to 7 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 25 Ventilator (Bear 750): N = 25 In both groups, CPAP was nasopharyngeal.
Outcomes	CPAP failure ("severe" intercostal retractions or prolonged apnoea (> 20 seconds) or persistent hypoxia, hypercarbia or acidosis with FiO_2 > 0.6 requiring mechanical ventilation) Death before discharge Duration of CPAP Duration of hospitalisation Pneumothorax (no events) Bronchopulmonary dysplasia Patent ductus arteriosus (confirmed by echocardiography) Intraventricular haemorrhage (grade III to IV) Nasal injury ("trauma to nasal septum and nostrils")
Notes	Setting: Kerman, Iran (2009 to 2010) Funding: Kerman University of Medical Sciences, Iran

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated (likely computer generated, as minimisation for gender and birthweight applied)
Allocation concealment (selection bias)	Unclear risk	Not stated; "randomly assigned"

Bahman-Bijari 2011 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Bhatti 2015

Study characteristics	
Methods	RCT
Participants	170 preterm neonates (< 34 weeks') with respiratory distress within 6 hours after birth treated with CPAP 5 to 7 cm H_2O (as primary support)
Interventions	Bubble ("stand-alone" system with Fisher & Paykel interface): N = 90 Ventilator (Jet-CPAP, Phoenix Medical Systems): N = 80 Short binasal prongs were the nasal interface.
Outcomes	CPAP failure within 72 hours (persistent hypoxia with FiO_2 > 0.6 requiring endotracheal intubation and mechanical ventilation or nasal intermittent positive pressure ventilation) Receipt of surfactant Death before discharge Duration of CPAP use Pneumothorax Bronchopulmonary dysplasia Retinopathy of prematurity Intraventricular haemorrhage (grade II to IV) Necrotising enterocolitis Nasal trauma (moderate-severe as per "Nasal Injury Score")
Notes	Setting: Chandigarh, India (2011 to 2012) Funding: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Bhatti 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generated ("web-based")
Allocation concealment (selection bias)	Low risk	Serially numbered, sealed, and opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Gupta 2009

Study characteristics	
Methods	RCT
Participants	140 preterm neonates (< 30 weeks' or birthweight 600 to 1500 g) ventilated at birth for respiratory distress, then treated with CPAP 6 cm H_2O (as postextubation support)
Interventions	Bubble (Fisher & Paykel): N = 71 Infant Flow Driver: N = 69 Nasal CPAP was delivered through short binasal prongs provided by the device manufacturers.
Outcomes	CPAP failure within 72 hours (endotracheal intubation and mechanical ventilation or nasal intermittent positive pressure ventilation) Death before discharge Duration of CPAP use Pneumothorax Bronchopulmonary dysplasia Patent ductus arteriosus (requiring treatment) Retinopathy of prematurity (requiring treatment) Intraventricular haemorrhage (grade III to IV) Necrotising enterocolitis
Notes	Setting: Middlesbrough, UK (2004 to 2007) Funding: not stated Trial registration number: ISRCTN 83339638

Gupta 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Serially numbered, sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Hosseini 2012

Study characteristics	
Methods	RCT
Participants	161 newborn infants (28 to 37 weeks' gestation) with respiratory distress (Silverman Score 5 to 6) up to 12 hours after birth treated with CPAP 5 to 6 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 71 Ventilator (Medijet): N = 90 Short binasal prongs were used in both groups.
Outcomes	CPAP failure (persistent hypoxia, hypercarbia or acidosis with FiO_2 > 0.5, or recurrent apnoea with bradycardia, and need for CPAP > 8 cm H_2O) Death before discharge Duration of CPAP use Duration of hospitalisation Pneumothorax Nasal trauma (columella necrosis) Intraventricular haemorrhage (grade III to IV) Feed intolerance Necrotising enterocolitis
Notes	Setting: Tabriz, Iran (2010 to 2011)

Hosseini 2012 *(Continued)*

	Funding: Medin Medical Innovations GMBH (Germany) and Pars Eltyam Kala (Iran)
	Trial registration number: IRCT138903174113N1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Unclear risk	Bubble CPAP group included fewer very low- and extremely low-birthweight or small-for-gestation infants than ventilator CPAP group.

Jazexhiu-Postoli 2015

Study characteristics

Methods	RCT
Participants	200 newborn infants (28 to 35 weeks' gestation) with respiratory distress up to 6 hours after birth treated with CPAP 6 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 100 Infant Flow Driver (biphasic): N = 100 Short binasal prongs were used in both groups.
Outcomes	CPAP failure (need for mechanical ventilation) Death before discharge Duration of CPAP use Pneumothorax Duration of hospitalisation (intensive care) Intraventricular haemorrhage (grade I to IV) Patent ductus arteriosus "Nasal lesions"

Jazexhiu-Postoli 2015 *(Continued)*

Notes	Setting: Tirana, Albania (2011 to 2013) Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated (corresponding author contacted September 2021)
Allocation concealment (selection bias)	Unclear risk	Not stated (corresponding author contacted September 2021)
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Unclear risk	Baseline characteristics data not reported.

Mazmanyan 2016

Study characteristics

Methods	RCT
Participants	125 preterm neonates (< 37 weeks') with respiratory distress treated with nasal CPAP 4 to 6 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 66 Infant Flow Driver: N = 59 Short binasal prongs were used for Infant Flow Driver CPAP, and pliable long anatomically curved prongs for bubble CPAP.
Outcomes	CPAP failure (receipt of mechanical ventilation) Death before discharge Duration of CPAP use Duration of supplemental oxygen Pneumothorax Nasal injury (excoriation) Retinopathy of prematurity Periventricular haemorrhage/leucomalacia

Mazmanyan 2016 *(Continued)*

	Necrotising enterocolitis
Notes	Setting: Yerevan, Armenia (2012 to 2014) Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Serially numbered, sealed, and opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Mazzella 2001

Study characteristics

Methods	RCT
Participants	36 preterm neonates (< 36 weeks') with respiratory distress up to 12 hours after birth treated with nasal CPAP 4 to 6 cm H_2O (as primary support)
Interventions	Bubble (single nasopharyngeal tube, pressure generated by underwater seal): N = 18 Infant Flow Driver: N = 18 Short binasal prongs were used for Infant Flow Driver CPAP, and a conventional single prong for bubble CPAP.
Outcomes	CPAP failure (need for mechanical ventilation) Death before discharge Duration of CPAP use Pneumothorax Bronchopulmonary dysplasia Intraventricular haemorrhage Nasal trauma (bleeding)

Mazzella 2001 *(Continued)*

Notes	Setting: Genova, Italy (1997 to 1999) Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Sealed, opaque, numbered envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Unclear risk	Infants in bubble CPAP group were of higher average gestational age at birth than those in Infant Flow Driver CPAP group (33 versus 32 weeks').

Mohammadizadeh 2011

Study characteristics

Methods	RCT
Participants	88 preterm neonates (29 to 33 weeks') with respiratory distress after birth treated with nasal CPAP up to 8 cm H_2O (as primary support)
Interventions	Bubble (manufacturer not stated): N = 44 Ventilator (Medijet): N = 44 Nasal interface not stated.
Outcomes	CPAP failure ("clinical or laboratory evidence of respiratory failure")* Surfactant administration via endotracheal tube (if FiO_2 > 0.4 with CPAP > 7 cm) Duration of CPAP use Duration of oxygen therapy Pneumothorax* Bronchopulmonary dysplasia*
Notes	Setting: Isfahan, Iran (pre-2011) Funding: not stated

Mohammadizadeh 2011 *(Continued)*

*Data not reported; author contacted September 2021.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	"randomly assigned"
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to determine
Selective reporting (reporting bias)	Unclear risk	Unable to determine
Other bias	Unclear risk	Unable to determine

Noori Shadkam 2017

Study characteristics	
Methods	RCT
Participants	119 preterm neonates (28 to 34 weeks' and birthweight of 1000 to 2200 g) with respiratory distress (Silverman score 5 to 7) treated with nasal CPAP 5 to 7 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 58 Ventilator (Stephan): N = 61 Nasal interface not stated.
Outcomes	Death before discharge Duration of CPAP use Duration of supplemental oxygen therapy Duration of hospitalisation Pneumothorax Patent ductus arteriosus (confirmed by echocardiography) Retinopathy of prematurity Intraventricular haemorrhage (grade III to IV) Bronchopulmonary dysplasia
Notes	Setting: Yazd, Iran (2013 to 2015)

Noori Shadkam 2017 *(Continued)*

	Funding: not stated Trial registration: IRCT2014081918862N1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables
Allocation concealment (selection bias)	Unclear risk	Not stated (author contacted September 2021)
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Ribeiro 2017

Study characteristics

Methods	RCT
Participants	65 preterm neonates (gestational age < 34 weeks and birthweight 500 to 1500 g) with respiratory distress treated surfactant replacement, then with CPAP 4 to 5 cm H_2O (as postextubation support)
Interventions	Bubble (manufacturer not stated): N = 32 Ventilator (InterMed): N = 33 Short binasal prongs were used in both groups.
Outcomes	CPAP failure within 48 hours of initiation (endotracheal re-intubation and mechanical ventilation) Death before discharge Pneumothorax Patent ductus arteriosus (confirmed by echocardiography) Bronchopulmonary dysplasia Duration of CPAP use Duration of oxygen supplementation Duration of hospitalisation Retinopathy of prematurity

Ribeiro 2017 *(Continued)*

	Intraventricular haemorrhage (grade III to IV)
	Necrotising enterocolitis
	Nasal injury (mild-moderate)*
Notes	Setting: São Paulo, Brazil (2012 to 2013)
	Funding: none
	NB. Erratum published.
	*Author contacted September 2021.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Tagare 2010

Study characteristics

Methods	RCT
Participants	30 preterm neonates (< 37 weeks') with respiratory distress (Silverman score 5 to 7) up to 6 hours after birth treated with nasal CPAP 5 to 7 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 15
	Ventilator (Bear Cub 750): N = 15
	Short binasal prongs were used in both groups.
Outcomes	Treatment failure (worsening respiratory distress with FiO_2 > 0.6 and CPAP > 8 cm H_2O)
	Duration of CPAP use
	Pneumothorax
	Nasal trauma (skin erosion/septal injury)

Tagare 2010 *(Continued)*

	(Mortality not reported.)
Notes	Setting: Pune, India (2007 to 2008) Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Serially numbered, sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Unclear risk	Few outcomes reported (pilot study).
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Tagare 2013

Study characteristics

Methods	RCT
Participants	114 preterm neonates (< 37 weeks') with respiratory distress (Silverman score > 3) up to 6 hours after birth treated with nasal CPAP 6 to 7 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 57 Ventilator (Bear Cub 750): N = 57 Short binasal prongs were used in both groups.
Outcomes	Treatment failure (worsening respiratory distress with FiO_2 > 0.6 and CPAP > 8 cm H_2O, recurrent apnoea, "shock", requiring endotracheal intubation and mechanical ventilation) Mortality before hospital discharge Duration of CPAP use Pneumothorax Nasal trauma (skin erosion/septal injury)
Notes	Setting: Pune, India (2008 to 2009)

Tagare 2013 *(Continued)*

	Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Sealed, coded envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Yadav 2012

Study characteristics

Methods	RCT
Participants	32 preterm neonates (< 33 weeks' and birthweight < 1500 g) ventilated within 1 week after birth for respiratory distress, then treated with CPAP 4 to 6 cm H_2O (as postextubation support)
Interventions	Bubble (Fisher & Paykel): N = 16 Ventilator (SLE 2000 or Dräger Babylog 8000): N = 16 Short binasal prongs were used in both groups.
Outcomes	CPAP failure within 72 hours of extubation (persistent hypoxia with FiO_2 > 0.6, recurrent apnoea and bradycardia, or systemic hypoperfusion requiring vasopressor therapy, requiring endotracheal intubation and mechanical ventilation) Pneumothorax Bronchopulmonary dysplasia Duration of hospitalisation Patent ductus arteriosus (confirmed by echocardiography) Retinopathy of prematurity Intraventricular haemorrhage (grade II to IV) Necrotising enterocolitis Culture-positive sepsis

Yadav 2012 *(Continued)*

	(Mortality not reported.)
Notes	Setting: New Dehli, India (2007 to 2009) Funding: Indian Council of Medical Research (equipment was provided by Fisher & Paykel)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Serially numbered, sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

Yagui 2011

Study characteristics

Methods	RCT
Participants	39 newborn infants* (birthweight > 1500 g) with respiratory distress within 24 hours after birth treated with CPAP 4 to 6 cm H_2O (as primary support)
Interventions	Bubble (Fisher & Paykel): N = 20 Ventilator (Siemens Servo – I): N = 19 Short binasal prongs were used in both groups.
Outcomes	CPAP failure (persistent hypoxia despite FiO_2 > 0.4 with CPAP > 8 cm H_2O requiring endotracheal intubation and mechanical ventilation) Pneumothorax Duration of CPAP use Duration of oxygen supplementation Duration of hospitalisation (Mortality not reported.)
Notes	Setting: São Paulo, Brazil (2008 to 2010)

Yagui 2011 *(Continued)*

Funding: not stated

*Mean gestation at birth 35 weeks'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Serially numbered, sealed, coded envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reporting complete.
Selective reporting (reporting bias)	Low risk	Unlikely (comprehensive; mortality not reported)
Other bias	Low risk	No evidence of an imbalance in baseline demographics

CPAP: continuous positive airway pressure
FiO_2: fraction of inspired oxygen
RCT: randomised controlled trial
VLBW: very low birthweight

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

Study	Reason for exclusion
Ahluwalia 1998	Cross-over study
Backes 2020	Randomised trial of 2 types of bubble CPAP (Seattle-PAP vs Fisher & Paykel CPAP)
Bhandari 1996	This comparison of nasal vs nasopharyngeal CPAP was non-randomised and retrospective.
Buettiker 2004	Assessed effect of nasopharyngeal CPAP (conventional ventilator) versus CPAP via Hudson (conventional ventilator) vs CPAP via Infant Flow Driver
Campbell 2006	Compared Infant Flow Driver CPAP with high-flow nasal cannulae
Courtney 2001	Cross-over study
Davis 2001	Trial compared effects of CPAP via Hudson prongs (conventional ventilator) vs CPAP via single prong (conventional ventilator).
Diala 2022	Non-randomised study
Guerin 2016	Cross-over study

Study	Reason for exclusion
Jonsson 1998	Cross-over study
Kavvadia 2000	Non-randomised study
Liptsen 2005	Cross-over study of bubble CPAP vs ventilator CPAP in preterm infants
Massaro 2005	Non-randomised study
Nair 2005	Assessed effect of high-flow nasal cannula system vs bubble CPAP
Narendran 2002	Non-randomised study (bubble CPAP vs ventilator CPAP)
Pandit 2001	Cross-over study
Pantalischka 2009	Cross-over study
Pelligra 2006	Non-randomised study (historical controls to compare bubble CPAP with ventilator CPAP)
Rego 2002	Trial comparing CPAP via Hudson vs Argyle prongs (both by conventional ventilator)
Roukema 1999a	Trial of Infant Flow Driver CPAP vs conventional ventilator nasopharyngeal CPAP
Roukema 1999b	Non-randomised evaluation of Infant Flow Driver CPAP vs conventional ventilator nasopharyngeal CPAP (postextubation)
Stefanescu 2003	Trial comparing Infant Flow CPAP vs ventilator CPAP (INCA binasal prongs)
Sun 1999	Randomised trial of Infant Flow Driver CPAP vs conventional ventilator CPAP
Tayler 2022	Non-randomised study
Telenko 1999	Cross-over study
Trevisanuto 2005	Compared Infant Flow nasal CPAP with CPAP delivered via a polycarbonate helmet

CPAP: continuous positive airway pressure

Characteristics of studies awaiting classification *[ordered by study ID]*

Colaizy 2004

Methods	Randomised controlled trial
Participants	Unknown
Interventions	"Bubble vs. conventional CPAP"
Outcomes	Unknown
Notes	Author contacted September 2021.

CPAP: continuous positive airway pressure

DATA AND ANALYSES

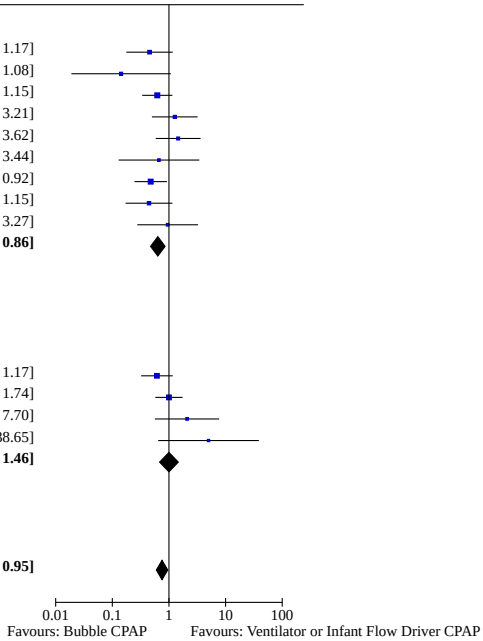
Comparison 1. Bubble CPAP versus ventilator or Infant Flow Driver CPAP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Treatment failure	13	1230	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.60, 0.95]
1.1.1 Bubble versus ventilator CPAP	9	729	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.47, 0.86]
1.1.2 Bubble versus Infant Flow Driver CPAP	4	501	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.46]
1.2 Mortality before discharge	10	1189	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.64, 1.36]
1.2.1 Bubble versus ventilator CPAP	6	688	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.52, 1.27]
1.2.2 Bubble versus Infant Flow Driver CPAP	4	501	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.63, 2.77]
1.3 Pneumothorax	14	1340	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.40, 1.34]
1.3.1 Bubble versus ventilator CPAP	10	839	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.27, 1.24]
1.3.2 Bubble versus Infant Flow Driver CPAP	4	501	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.40, 3.16]
1.4 Moderate-severe nasal injury	8	753	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.37, 3.82]
1.4.1 Bubble versus ventilator CPAP	6	592	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [1.49, 4.53]
1.4.2 Bubble versus Infant Flow Driver CPAP	2	161	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.21, 3.99]
1.5 Bronchopulmonary dysplasia	7	603	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.53, 1.10]
1.5.1 Bubble versus ventilator CPAP	5	427	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.52, 1.35]
1.5.2 Bubble versus Infant Flow Driver CPAP	2	176	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.17]
1.6 Duration of CPAP use	8	744	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.16, 0.13]
1.6.1 Bubble versus ventilator CPAP	6	508	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.12, 0.19]
1.6.2 Bubble versus Infant Flow Driver CPAP	2	236	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-1.07, -0.05]
1.7 Duration of oxygen supplementation	1	88	Mean Difference (IV, Fixed, 95% CI)	0.60 [-2.52, 3.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Bubble versus ventilator CPAP	1	88	Mean Difference (IV, Fixed, 95% CI)	0.60 [-2.52, 3.72]
1.8 Duration of hospitalisation	5	591	Mean Difference (IV, Fixed, 95% CI)	-3.27 [-4.99, -1.56]
1.8.1 Bubble versus ventilator CPAP	4	391	Mean Difference (IV, Fixed, 95% CI)	-2.61 [-4.52, -0.70]
1.8.2 Bubble versus Infant Flow Driver CPAP	1	200	Mean Difference (IV, Fixed, 95% CI)	-6.00 [-9.88, -2.12]
1.9 Patent ductus arteriosus	6	597	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.67, 1.38]
1.9.1 Bubble versus ventilator CPAP	4	257	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.61, 2.35]
1.9.2 Bubble versus Infant Flow Driver CPAP	2	340	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.35]
1.10 Necrotising enterocolitis	6	693	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.39, 1.44]
1.10.1 Bubble versus ventilator CPAP	4	428	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.28, 1.37]
1.10.2 Bubble versus Infant Flow Driver CPAP	2	265	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.35, 3.92]
1.11 Severe intraventricular haemorrhage	6	562	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.42, 1.58]
1.11.1 Bubble versus ventilator CPAP	3	321	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.12, 1.39]
1.11.2 Bubble versus Infant Flow Driver CPAP	3	241	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.53, 2.69]
1.12 Severe retinopathy of prematurity	6	642	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.54, 1.57]
1.12.1 Bubble versus ventilator CPAP	4	377	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.53, 1.72]
1.12.2 Bubble versus Infant Flow Driver CPAP	2	265	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.22, 2.77]

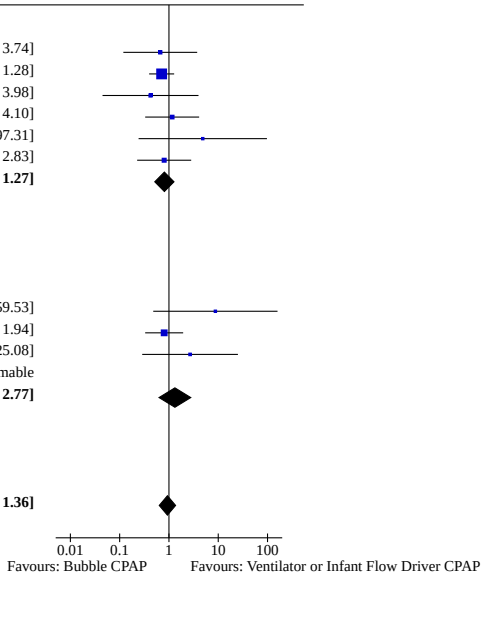
Analysis 1.1. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 1: Treatment failure

Study or Subgroup	Bubble CPAP Events	Bubble CPAP Total	Ventilator or Infant Flow Driver CPAP Events	Ventilator or Infant Flow Driver CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Bubble versus ventilator CPAP						
Agarwal 2016	5	34	11	34	8.3%	0.45 [0.18 , 1.17]
Bahman-Bijari 2011	1	25	7	25	5.3%	0.14 [0.02 , 1.08]
Bhatti 2015	14	90	20	80	15.9%	0.62 [0.34 , 1.15]
Hosseini 2012	8	71	8	90	5.3%	1.27 [0.50 , 3.21]
Ribeiro 2017	9	33	6	32	4.6%	1.45 [0.58 , 3.62]
Tagare 2010	2	15	3	15	2.3%	0.67 [0.13 , 3.44]
Tagare 2013	10	57	21	57	15.8%	0.48 [0.25 , 0.92]
Yadav 2012	4	16	9	16	6.8%	0.44 [0.17 , 1.15]
Yagui 2011	4	20	4	19	3.1%	0.95 [0.28 , 3.27]
Subtotal (95% CI)		**361**		**368**	**67.3%**	**0.64 [0.47 , 0.86]**
Total events:	57		89			
Heterogeneity: Chi² = 9.57, df = 8 (P = 0.30); I² = 16%						
Test for overall effect: Z = 3.00 (P = 0.003)						
1.1.2 Bubble versus Infant Flow Driver CPAP						
Gupta 2009	12	71	19	69	14.5%	0.61 [0.32 , 1.17]
Jazexhiu-Postoli 2015	20	100	20	100	15.1%	1.00 [0.57 , 1.74]
Mazmanyan 2016	7	66	3	59	2.4%	2.09 [0.56 , 7.70]
Mazzella 2001	5	18	1	18	0.8%	5.00 [0.65 , 38.65]
Subtotal (95% CI)		**255**		**246**	**32.7%**	**1.00 [0.68 , 1.46]**
Total events:	44		43			
Heterogeneity: Chi² = 5.81, df = 3 (P = 0.12); I² = 48%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**616**		**614**	**100.0%**	**0.76 [0.60 , 0.95]**
Total events:	101		132			
Heterogeneity: Chi² = 17.51, df = 12 (P = 0.13); I² = 31%						
Test for overall effect: Z = 2.37 (P = 0.02)						
Test for subgroup differences: Chi² = 3.38, df = 1 (P = 0.07), I² = 70.4%						



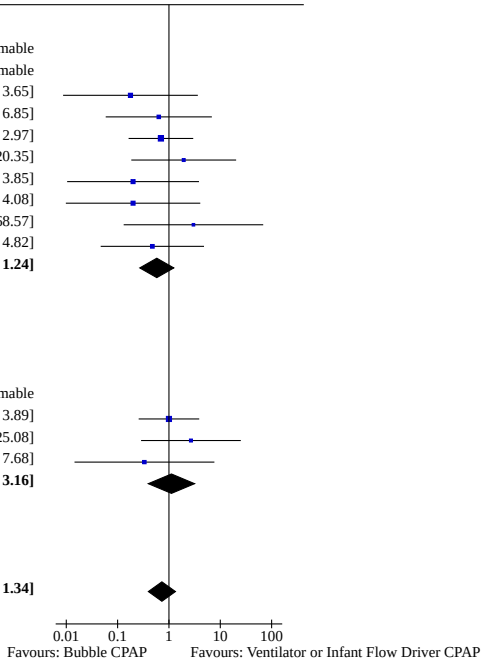
Analysis 1.2. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 2: Mortality before discharge

Study or Subgroup	Bubble CPAP Events	Bubble CPAP Total	Ventilator or Infant Flow Driver CPAP Events	Ventilator or Infant Flow Driver CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Bubble versus ventilator CPAP						
Agarwal 2016	2	34	3	34	6.2%	0.67 [0.12 , 3.74]
Bhatti 2015	16	90	20	80	44.1%	0.71 [0.40 , 1.28]
Hosseini 2012	1	71	3	90	5.5%	0.42 [0.04 , 3.98]
Noori Shadkam 2017	5	57	4	53	8.6%	1.16 [0.33 , 4.10]
Ribeiro 2017	2	33	0	32	1.1%	4.85 [0.24 , 97.31]
Tagare 2013	4	57	5	57	10.4%	0.80 [0.23 , 2.83]
Subtotal (95% CI)		**342**		**346**	**75.9%**	**0.81 [0.52 , 1.27]**
Total events:	30		35			
Heterogeneity: Chi² = 2.25, df = 5 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
1.2.2 Bubble versus Infant Flow Driver CPAP						
Gupta 2009	4	71	0	69	1.1%	8.75 [0.48 , 159.53]
Jazexhiu-Postoli 2015	8	100	10	100	20.8%	0.80 [0.33 , 1.94]
Mazmanyan 2016	3	66	1	59	2.2%	2.68 [0.29 , 25.08]
Mazzella 2001	0	18	0	18		Not estimable
Subtotal (95% CI)		**255**		**246**	**24.1%**	**1.32 [0.63 , 2.77]**
Total events:	15		11			
Heterogeneity: Chi² = 3.24, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**597**		**592**	**100.0%**	**0.93 [0.64 , 1.36]**
Total events:	45		46			
Heterogeneity: Chi² = 6.04, df = 8 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.2%						



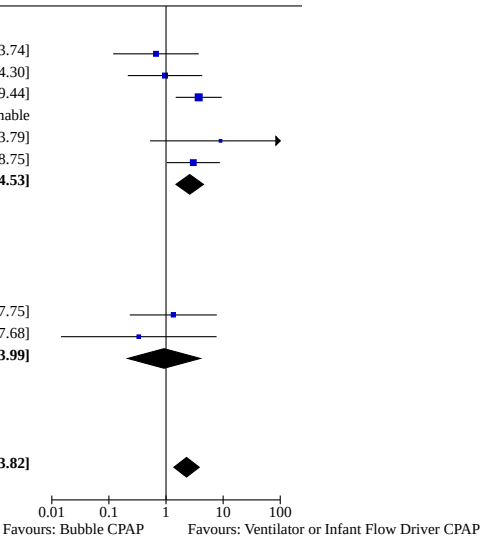
Analysis 1.3. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 3: Pneumothorax

Study or Subgroup	Bubble CPAP Events	Bubble CPAP Total	Ventilator or Infant Flow Driver CPAP Events	Ventilator or Infant Flow Driver CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Bubble versus ventilator CPAP						
Agarwal 2016	0	34	0	34		Not estimable
Bahman-Bijari 2011	0	25	0	25		Not estimable
Bhatti 2015	0	90	2	80	11.2%	0.18 [0.01 , 3.65]
Hosseini 2012	1	71	2	90	7.5%	0.63 [0.06 , 6.85]
Noori Shadkam 2017	3	57	4	53	17.5%	0.70 [0.16 , 2.97]
Ribeiro 2017	2	33	1	32	4.3%	1.94 [0.18 , 20.35]
Tagare 2010	0	15	2	15	10.6%	0.20 [0.01 , 3.85]
Tagare 2013	0	57	2	57	10.6%	0.20 [0.01 , 4.08]
Yadav 2012	1	16	0	16	2.1%	3.00 [0.13 , 68.57]
Yagui 2011	1	20	2	19	8.7%	0.47 [0.05 , 4.82]
Subtotal (95% CI)		**418**		**421**	**72.3%**	**0.58 [0.27 , 1.24]**
Total events:	8		15			
Heterogeneity: Chi² = 3.73, df = 7 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
1.3.2 Bubble versus Infant Flow Driver CPAP						
Gupta 2009	0	71	0	69		Not estimable
Jazexhiu-Postoli 2015	4	100	4	100	16.9%	1.00 [0.26 , 3.89]
Mazmanyan 2016	3	66	1	59	4.5%	2.68 [0.29 , 25.08]
Mazzella 2001	0	18	1	18	6.3%	0.33 [0.01 , 7.68]
Subtotal (95% CI)		**255**		**246**	**27.7%**	**1.12 [0.40 , 3.16]**
Total events:	7		6			
Heterogeneity: Chi² = 1.19, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Total (95% CI)		**673**		**667**	**100.0%**	**0.73 [0.40 , 1.34]**
Total events:	15		21			
Heterogeneity: Chi² = 5.63, df = 10 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 1.00, df = 1 (P = 0.32), I² = 0%						



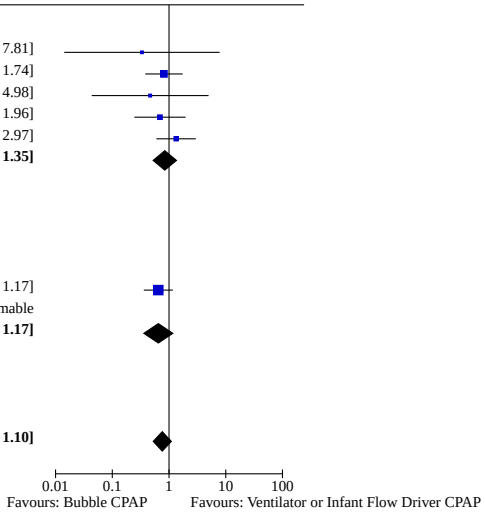
Analysis 1.4. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 4: Moderate-severe nasal injury

Study or Subgroup	Bubble CPAP Events	Bubble CPAP Total	Ventilator or Infant Flow Driver CPAP Events	Ventilator or Infant Flow Driver CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Bubble versus ventilator CPAP						
Agarwal 2016	2	34	3	34	15.4%	0.67 [0.12 , 3.74]
Bahman-Bijari 2011	3	25	3	24	15.7%	0.96 [0.21 , 4.30]
Bhatti 2015	21	90	5	80	27.2%	3.73 [1.48 , 9.44]
Hosseini 2012	0	71	0	90		Not estimable
Tagare 2010	4	15	0	15	2.6%	9.00 [0.53 , 153.79]
Tagare 2013	12	57	4	57	20.5%	3.00 [1.03 , 8.75]
Subtotal (95% CI)		**292**		**300**	**81.4%**	**2.60 [1.49 , 4.53]**
Total events:	42		15			
Heterogeneity: Chi² = 5.48, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 3.37 (P = 0.0007)						
1.4.2 Bubble versus Infant Flow Driver CPAP						
Mazmanyan 2016	3	66	2	59	10.8%	1.34 [0.23 , 7.75]
Mazzella 2001	0	18	1	18	7.7%	0.33 [0.01 , 7.68]
Subtotal (95% CI)		**84**		**77**	**18.6%**	**0.92 [0.21 , 3.99]**
Total events:	3		3			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		**376**		**377**	**100.0%**	**2.29 [1.37 , 3.82]**
Total events:	45		18			
Heterogeneity: Chi² = 7.27, df = 6 (P = 0.30); I² = 17%						
Test for overall effect: Z = 3.17 (P = 0.002)						
Test for subgroup differences: Chi² = 1.68, df = 1 (P = 0.19), I² = 40.5%						



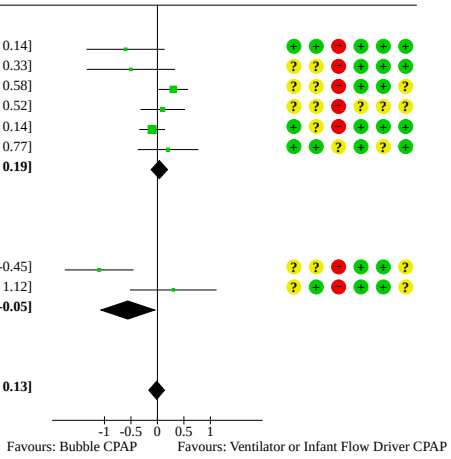
Analysis 1.5. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 5: Bronchopulmonary dysplasia

Study or Subgroup	Bubble CPAP Events	Bubble CPAP Total	Ventilator or Infant Flow Driver CPAP Events	Ventilator or Infant Flow Driver CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Bubble versus ventilator CPAP						
Bahman-Bijari 2011	0	25	1	25	3.0%	0.33 [0.01 , 7.81]
Bhatti 2015	11	90	12	80	25.1%	0.81 [0.38 , 1.74]
Noori Shadkam 2017	1	57	2	53	4.1%	0.46 [0.04 , 4.98]
Ribeiro 2017	5	33	7	32	14.0%	0.69 [0.24 , 1.96]
Yadav 2012	8	16	6	16	11.8%	1.33 [0.60 , 2.97]
Subtotal (95% CI)		**221**		**206**	**58.0%**	**0.84 [0.52 , 1.35]**
Total events:	25		28			
Heterogeneity: Chi² = 1.98, df = 4 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.5.2 Bubble versus Infant Flow Driver CPAP						
Gupta 2009	14	71	21	69	42.0%	0.65 [0.36 , 1.17]
Mazzella 2001	0	18	0	18		Not estimable
Subtotal (95% CI)		**89**		**87**	**42.0%**	**0.65 [0.36 , 1.17]**
Total events:	14		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
Total (95% CI)		**310**		**293**	**100.0%**	**0.76 [0.53 , 1.10]**
Total events:	39		49			
Heterogeneity: Chi² = 2.67, df = 5 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.15)						
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%						



Analysis 1.6. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 6: Duration of CPAP use

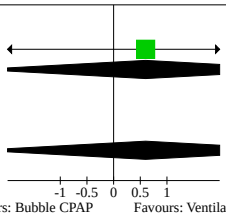
Study or Subgroup	Bubble CPAP Mean	Bubble CPAP SD	Bubble CPAP Total	Ventilator or Infant Flow Driver CPAP Mean	Ventilator or Infant Flow Driver CPAP SD	Ventilator or Infant Flow Driver CPAP Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.6.1 Bubble versus ventilator CPAP														
Agarwal 2016	2	1.1	34	2.6	1.9	34	4.0%	-0.60 [-1.34 , 0.14]	+	+	−	+	+	+
Bahman-Bijari 2011	1.6	1.6	25	2.1	1.4	25	3.2%	-0.50 [-1.33 , 0.33]	?	?	−	+	+	+
Hosseini 2012	2.1	0.9	71	1.8	0.9	91	28.1%	0.30 [0.02 , 0.58]	?	?	−	+	+	?
Mohammadizadeh 2011	2	1.1	44	1.9	0.9	44	12.4%	0.10 [-0.32 , 0.52]	?	?	−	?	?	?
Noori Shadkam 2017	2.1	0.7	57	2.2	0.6	53	37.1%	-0.10 [-0.34 , 0.14]	+	?	−	+	+	+
Tagare 2010	1.1	0.8	15	0.9	0.8	15	6.7%	0.20 [-0.37 , 0.77]	+	+	?	+	?	+
Subtotal (95% CI)			**246**			**262**	**91.5%**	**0.04 [-0.12 , 0.19]**						
Heterogeneity: Chi² = 9.48, df = 5 (P = 0.09); I² = 47%														
Test for overall effect: Z = 0.46 (P = 0.65)														
1.6.2 Bubble versus Infant Flow Driver CPAP														
Jazexhiu-Postoli 2015	2.1	1.6	100	3.2	2.9	100	5.2%	-1.10 [-1.75 , -0.45]	?	?	−	+	+	?
Mazzella 2001	2.4	1.2	18	2.1	1.3	18	3.3%	0.30 [-0.52 , 1.12]	?	+	−	+	+	?
Subtotal (95% CI)			**118**			**118**	**8.5%**	**-0.56 [-1.07 , -0.05]**						
Heterogeneity: Chi² = 6.91, df = 1 (P = 0.009); I² = 86%														
Test for overall effect: Z = 2.15 (P = 0.03)														
Total (95% CI)			**364**			**380**	**100.0%**	**-0.01 [-0.16 , 0.13]**						
Heterogeneity: Chi² = 21.20, df = 7 (P = 0.003); I² = 67%														
Test for overall effect: Z = 0.19 (P = 0.85)														
Test for subgroup differences: Chi² = 4.81, df = 1 (P = 0.03), I² = 79.2%														



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

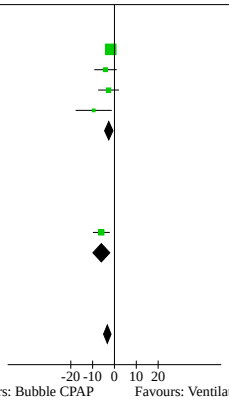
Analysis 1.7. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 7: Duration of oxygen supplementation

Study or Subgroup	Bubble CPAP Mean	SD	Total	Ventilator or Infant Flow Driver CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 Bubble versus ventilator CPAP								
Mohammadizadeh 2011	6.6	8	44	6	6.9	44	100.0%	0.60 [-2.52 , 3.72]
Subtotal (95% CI)			**44**			**44**	**100.0%**	**0.60 [-2.52 , 3.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.71)								
Total (95% CI)			**44**			**44**	**100.0%**	**0.60 [-2.52 , 3.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.71)								
Test for subgroup differences: Not applicable								



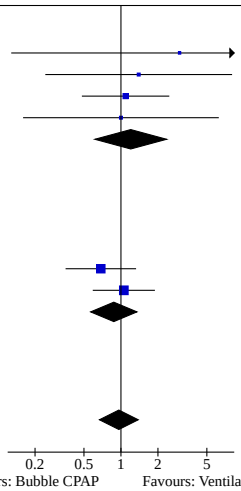
Analysis 1.8. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 8: Duration of hospitalisation

Study or Subgroup	Bubble CPAP Mean	SD	Total	Ventilator or Infant Flow Driver CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 Bubble versus ventilator CPAP								
Bahman-Bijari 2011	8.9	3.4	44	10.6	7.3	44	52.0%	-1.70 [-4.08 , 0.68]
Hosseini 2012	22.1	14.3	71	26.2	19	90	11.1%	-4.10 [-9.25 , 1.05]
Noori Shadkam 2017	20.1	13.6	57	22.8	11.8	53	13.0%	-2.70 [-7.45 , 2.05]
Yadav 2012	50.5	10.8	16	60	13	16	4.3%	-9.50 [-17.78 , -1.22]
Subtotal (95% CI)			**188**			**203**	**80.4%**	**-2.61 [-4.52 , -0.70]**
Heterogeneity: Chi² = 3.54, df = 3 (P = 0.32); I² = 15%								
Test for overall effect: Z = 2.67 (P = 0.007)								
1.8.2 Bubble versus Infant Flow Driver CPAP								
Jazexhiu-Postoli 2015	10.7	10.6	100	16.7	16.7	100	19.6%	-6.00 [-9.88 , -2.12]
Subtotal (95% CI)			**100**			**100**	**19.6%**	**-6.00 [-9.88 , -2.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.03 (P = 0.002)								
Total (95% CI)			**288**			**303**	**100.0%**	**-3.27 [-4.99 , -1.56]**
Heterogeneity: Chi² = 5.91, df = 4 (P = 0.21); I² = 32%								
Test for overall effect: Z = 3.74 (P = 0.0002)								
Test for subgroup differences: Chi² = 2.36, df = 1 (P = 0.12), I² = 57.7%								



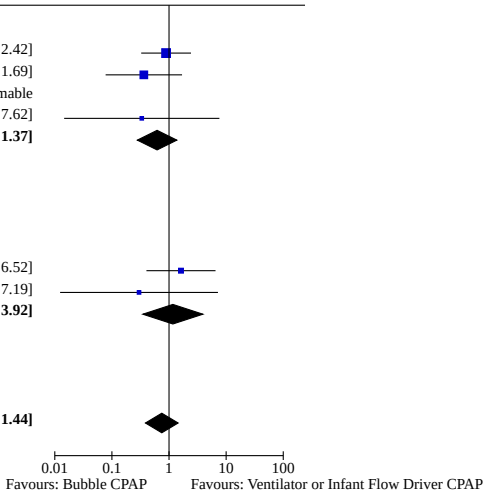
Analysis 1.9. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 9: Patent ductus arteriosus

Study or Subgroup	Bubble CPAP Events	Total	Ventilator or Infant Flow Driver CPAP Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Bubble versus ventilator CPAP						
Bahman-Bijari 2011	1	25	0	25	1.0%	3.00 [0.13 , 70.30]
Noori Shadkam 2017	3	57	2	53	4.3%	1.39 [0.24 , 8.02]
Ribeiro 2017	9	33	8	32	16.9%	1.09 [0.48 , 2.47]
Yadav 2012	2	16	2	16	4.2%	1.00 [0.16 , 6.25]
Subtotal (95% CI)		**131**		**126**	**26.5%**	**1.20 [0.61 , 2.35]**
Total events:	15		12			
Heterogeneity: Chi² = 0.44, df = 3 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						
1.9.2 Bubble versus Infant Flow Driver CPAP						
Gupta 2009	12	71	17	69	36.0%	0.69 [0.35 , 1.33]
Jazexhiu-Postoli 2015	19	100	18	100	37.5%	1.06 [0.59 , 1.89]
Subtotal (95% CI)		**171**		**169**	**73.5%**	**0.87 [0.57 , 1.35]**
Total events:	31		35			
Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**302**		**295**	**100.0%**	**0.96 [0.67 , 1.38]**
Total events:	46		47			
Heterogeneity: Chi² = 1.87, df = 5 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%						



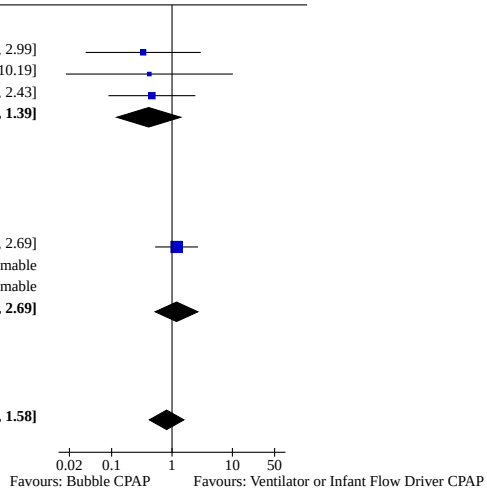
Analysis 1.10. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 10: Necrotising enterocolitis

Study or Subgroup	Bubble CPAP Events	Bubble CPAP Total	Ventilator or Infant Flow Driver CPAP Events	Ventilator or Infant Flow Driver CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Bubble versus ventilator CPAP						
Bhatti 2015	7	90	7	80	37.6%	0.89 [0.33 , 2.42]
Hosseini 2012	2	71	7	90	31.3%	0.36 [0.08 , 1.69]
Ribeiro 2017	0	33	0	32		Not estimable
Yadav 2012	0	16	1	16	7.6%	0.33 [0.01 , 7.62]
Subtotal (95% CI)		**210**		**218**	**76.5%**	**0.62 [0.28 , 1.37]**
Total events:	9		15			
Heterogeneity: Chi² = 1.12, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.10.2 Bubble versus Infant Flow Driver CPAP						
Gupta 2009	5	71	3	69	15.4%	1.62 [0.40 , 6.52]
Mazmanyan 2016	0	66	1	59	8.0%	0.30 [0.01 , 7.19]
Subtotal (95% CI)		**137**		**128**	**23.5%**	**1.17 [0.35 , 3.92]**
Total events:	5		4			
Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
Total (95% CI)		**347**		**346**	**100.0%**	**0.75 [0.39 , 1.44]**
Total events:	14		19			
Heterogeneity: Chi² = 2.73, df = 4 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.39)						
Test for subgroup differences: Chi² = 0.74, df = 1 (P = 0.39), I² = 0%						

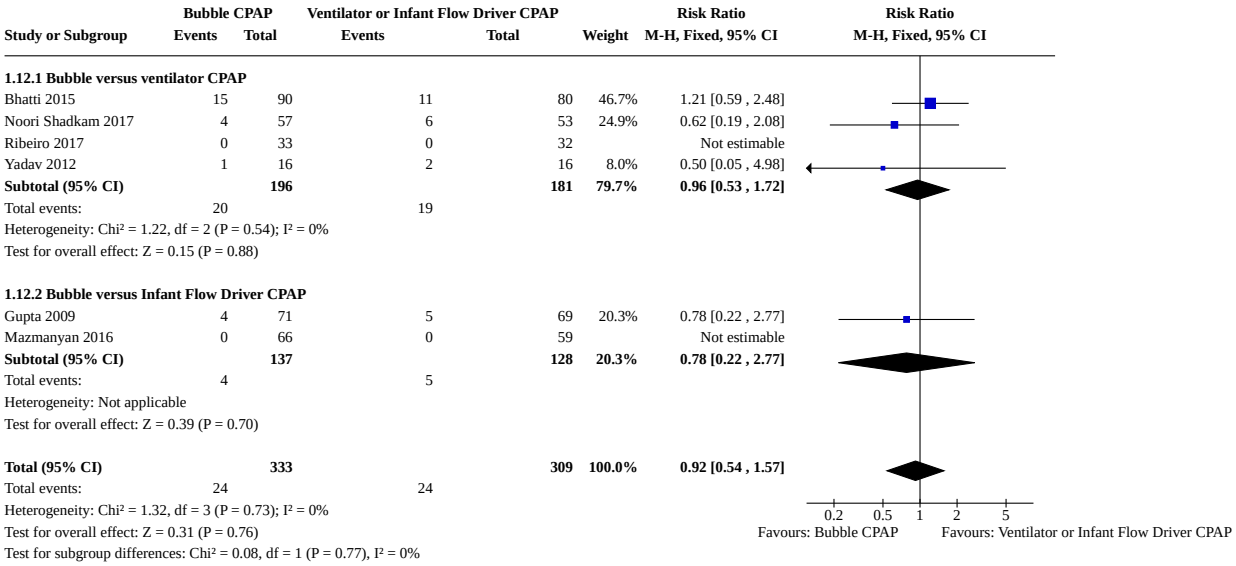


Analysis 1.11. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 11: Severe intraventricular haemorrhage

Study or Subgroup	Bubble CPAP Events	Bubble CPAP Total	Ventilator or Infant Flow Driver CPAP Events	Ventilator or Infant Flow Driver CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Bubble versus ventilator CPAP						
Bahman-Bijari 2011	1	25	3	25	17.0%	0.33 [0.04 , 2.99]
Hosseini 2012	0	71	1	90	7.5%	0.42 [0.02 , 10.19]
Noori Shadkam 2017	2	57	4	53	23.6%	0.46 [0.09 , 2.43]
Subtotal (95% CI)		**153**		**168**	**48.1%**	**0.41 [0.12 , 1.39]**
Total events:	3		8			
Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
1.11.2 Bubble versus Infant Flow Driver CPAP						
Gupta 2009	11	71	9	69	51.9%	1.19 [0.53 , 2.69]
Mazzella 2001	0	18	0	18		Not estimable
Ribeiro 2017	0	33	0	32		Not estimable
Subtotal (95% CI)		**122**		**119**	**51.9%**	**1.19 [0.53 , 2.69]**
Total events:	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**275**		**287**	**100.0%**	**0.81 [0.42 , 1.58]**
Total events:	14		17			
Heterogeneity: Chi² = 2.06, df = 3 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: Chi² = 2.01, df = 1 (P = 0.16), I² = 50.2%						



Analysis 1.12. Comparison 1: Bubble CPAP versus ventilator or Infant Flow Driver CPAP, Outcome 12: Severe retinopathy of prematurity



APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) strategy

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Date range: Issue 12 of 12, December 2022

Date searched: 6th January 2023

Records retrieved: 2763

#1 [mh "Infant, Newborn"] 17815

#2 [mh ^"Premature Birth"] 1827

#3 (neonat* or neo NEXT nat*):ti,ab,kw 26271

#4 (newborn* or new NEXT born* or newly NEXT born*):ti,ab,kw 31671

#5 (preterm or preterms or pre NEXT term*1):ti,ab,kw 15821

#6 (preemie* or premie or premies):ti,ab,kw 56

#7 (prematur* NEAR/3 (birth* or born or deliver*)):ti,ab,kw 3471

#8 (low NEAR/3 (birthweight* or birth NEXT weight*)):ti,ab,kw 5996

#9 low NEXT birthweight*:ti,ab,kw 969

#10 (LBW or VLBW or ELBW):ti,ab,kw 1845

#11 infan*:ti,ab,kw 71072

#12 (baby or babies):ti,ab,kw 10445

#13 {OR #1-#12} 90884

#14 [mh "Positive-Pressure Respiration"] 3068

#15 ((((continuous* or positive) NEAR/3 pressure*) or (positive NEXT pressure* or PAP)) and (airway* or air NEXT way* or breath*1 or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)):ti,ab,kw 11077

#16 (((airway* or air NEXT way*) NEAR/3 pressure*) and (breath*1 or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)):ti,ab,kw 6212

#17 ((PPV or CPAP or C NEXT PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (airway* or air NEXT way* or breath*1 or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)):ti,ab,kw 5677

#18 ((((continuous* or positive or airway* or air NEXT way*) NEAR/3 pressure*) or positive NEXT pressure*) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face NEXT mask* or headgear* or head NEXT gear or headbox or head NEXT box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth NEXT piece* or nebuli?er* or prong*1)):ti,ab,kw 4175

#19 ((PAP or PPV or CPAP or C NEXT PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face NEXT mask* or headgear* or head NEXT gear or headbox or head NEXT box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth NEXT piece* or nebuli?er* or prong*1)):ti,ab,kw 2516

#20 {OR #14-#19} 14058

#21 #13 AND #20 in Trials 2763

Key:

mh = exploded indexing term (MeSH)

mh ^ = indexing term (MeSH)

* = truncation

? = one additional letter

ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other.

Appendix 2. MEDLINE strategy

Ovid MEDLINE(R) ALL

via Ovid http://ovidsp.ovid.com/

Date range searched: <1946 to January 05, 2023>

Date searched: 6th January 2023

Records retrieved: 2414

1 exp Infant, Newborn/ (664702)

2 Premature Birth/ (19913)

3 (neonat* or neo nat* or neo-nat*).ti,ab,kw,kf. (306658)

4 (newborn* or new born* or new-born* or newly born* or newly-born*).ti,ab,kw,kf. (199194)

5 (preterm or preterms or pre term or pre terms or pre-term or pre-terms).ti,ab,kw,kf. (92142)

6 (preemie* or premie or premies).ti,ab,kw,kf. (217)

7 (prematur* adj3 (birth* or born or deliver*)).ti,ab,kw,kf. (18646)

8 (low adj3 (birthweight* or birth weight* or birth-weight*)).ti,ab,kw,kf. (40109)

9 low-birthweight*.ti,ab,kw,kf. (8462)

10 (LBW or VLBW or ELBW).ti,ab,kw,kf. (10131)

11 infan*.ti,ab,kw,kf. (541458)

12 (baby or babies).ti,ab,kw,kf. (79472)

13 or/1-12 (1204779)

14 exp Positive-Pressure Respiration/ (28759)

15 ((((continuous* or positive) adj3 pressure*) or (positive-pressure* or PAP)) and (airway* or air-way* or breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,kw,kf. (31221)

16 (((airway* or air-way*) adj3 pressure*) and (breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,kw,kf. (14702)

17 ((PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (airway* or air-way* or breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,kw,kf. (12732)

18 ((((continuous* or positive or airway* or air-way*) adj3 pressure*) or positive-pressure*) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong?)).ti,ab,kw,kf. (8333)

19 ((PAP or PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong?)).ti,ab,kw,kf. (7027)

20 or/14-19 (54118)

21 13 and 20 (8193)

22 randomized controlled trial.pt. (583819)

23 controlled clinical trial.pt. (95151)

24 randomized.ab. (587721)

25 placebo.ab. (234504)

26 drug therapy.fs. (2559741)

27 randomly.ab. (398865)

28 trial.ab. (629833)

29 groups.ab. (2456292)

30 or/22-29 (5549711)

31 21 and 30 (2651)

32 exp animals/ not humans.sh. (5079099)

33 31 not 32 (2454)

34 remove duplicates from 33 (2414)

Key:

/ or.sh. = indexing term (Medical Subject Heading: MeSH)

exp = exploded indexing term (MeSH)

$ or * = truncation

? = one additional letter

ti,ab,kw,kf = terms in either title, abstract, keyword heading or keyword heading word fields

fs = floating subheading

adj3 = terms within three words of each other (any order).

pt = publication type

Appendix 3. Embase strategy

Embase

via Ovid http://ovidsp.ovid.com/

Date range searched: < 1974 to 2023 January 05>

Date searched: 6th January 2023

Records retrieved: 3438

1 exp infant/ (1102101)

2 prematurity/ (120734)

3 (neonat* or neo nat* or neo-nat*).ti,ab,kw,kf. (401481)

4 (newborn* or new born* or new-born* or newly born* or newly-born*).ti,ab,kw,kf. (225075)

5 (preterm or preterms or pre term or pre terms or pre-term or pre-terms).ti,ab,kw,kf. (130056)

6 (preemie* or premie or premies).ti,ab,kw,kf. (351)

7 (prematur* adj3 (birth* or born or deliver*)).ti,ab,kw,kf. (26326)

8 (low adj3 (birthweight* or birth weight* or birth-weight*)).ti,ab,kw,kf. (51868)

9 low-birthweight*.ti,ab,kw,kf. (10263)

10 (LBW or VLBW or ELBW).ti,ab,kw,kf. (13973)

11 infan*.ti,ab,kw,kf. (574778)

12 (baby or babies).ti,ab,kw,kf. (111989)

13 or/1-12 (1566468)

14 exp positive pressure ventilation/ (17447)

15 ((((continuous* or positive) adj3 pressure*) or (positive-pressure* or PAP)) and (airway* or air-way* or breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,kw,kf. (45629)

16 (((airway* or air-way*) adj3 pressure*) and (breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,kw,kf. (21835)

17 ((PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (airway* or air-way* or breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,kw,kf. (23786)

18 ((((continuous* or positive or airway* or air-way*) adj3 pressure*) or positive-pressure*) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong?)).ti,ab,kw,kf. (13046)

19 ((PAP or PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong?)).ti,ab,kw,kf. (13399)

20 or/14-19 (77182)

21 13 and 20 (11985)

22 randomized controlled trial/ (744605)

23 controlled clinical trial/ (467918)

24 Random$.ti,ab,ot. (1876296)

25 randomization/ (95926)

26 intermethod comparison/ (291127)

27 placebo.ti,ab,ot. (352175)

28 (compare or compared or comparison).ti,ot. (583643)

29 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2630778)

30 (open adj label).ti,ab,ot. (102877)

31 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,ot. (264696)

32 double blind procedure/ (202377)

33 parallel group$1.ti,ab,ot. (30678)

34 (crossover or cross over).ti,ab,ot. (120062)

35 ((assign$ or match or matched or allocation) adj5 (alternate or group or groups or intervention or interventions or patient or patients or subject or subjects or participant or participants)).ti,ab,ot. (396360)

36 (assigned or allocated).ti,ab,ot. (467774)

37 (controlled adj7 (study or design or trial)).ti,ab,ot. (428081)

38 (volunteer or volunteers).ti,ab,ot. (274706)

39 human experiment/ (609337)

40 trial.ti,ot. (379354)

41 or/22-40 (6032343)

42 21 and 41 (3808)

43 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$).ti,ot. and animal experiment/ (1181493)

44 Animal experiment/ not (human experiment/ or human/) (2480517)

45 43 or 44 (2544025)

46 42 not 45 (3533)

47 remove duplicates from 46 (3438)

Key:

/ or.sh. = indexing term (Emtree Subject Heading)

exp = exploded indexing term (Emtree)

$ or * = truncation

? = one additional letter

ti,ab,kw,kf = terms in either title, abstract, keyword heading or keyword heading word fields

adj3 = terms within three words of each other (any order).

pt = publication type

ot = original title

Appendix 4. MIDIRS strategy

Maternity & Infant Care Database (MIDIRS)

via Ovid http://ovidsp.ovid.com/

Date range searched: <1971 to December 13, 2022>

Date searched: 6th January 2023

Records retrieved: 143

1 (neonat* or neo nat* or neo-nat*).ti,ab,hw,de. (57665)

2 (newborn* or new born* or new-born* or newly born* or newly-born*).ti,ab,hw,de. (45135)

3 (preterm or preterms or pre term or pre terms or pre-term or pre-terms).ti,ab,hw,de. (32763)

4 (preemie* or premie or premies).ti,ab,hw,de. (68)

5 (prematur* adj3 (birth* or born or deliver*)).ti,ab,hw,de. (7706)

6 (low adj3 (birthweight* or birth weight* or birth-weight*)).ti,ab,hw,de. (13479)

7 low-birthweight*.ti,ab,hw,de. (3490)

8 (LBW or VLBW or ELBW).ti,ab,hw,de. (3643)

9 infan*.ti,ab,hw,de. (101933)

10 (baby or babies).ti,ab,hw,de. (33202)

11 or/1-10 (152409)

12 ((((continuous* or positive) adj3 pressure*) or (positive-pressure* or PAP)) and (airway* or air-way* or breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,hw,de. (1465)

13 (((airway* or air-way*) adj3 pressure*) and (breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,hw,de. (1092)

14 ((PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (airway* or air-way* or breath? or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)).ti,ab,hw,de. (794)

15 ((((continuous* or positive or airway* or air-way*) adj3 pressure*) or positive-pressure*) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong?)).ti,ab,hw,de. (396)

16 ((PAP or PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong?)).ti,ab,hw,de. (259)

17 or/12-16 (1768)

18 11 and 17 (1699)

19 limit 18 to randomised controlled trial (143)

Key:

/ or.sh. = indexing term (Emtree Subject Heading)

exp = exploded indexing term (Emtree)

$ or * = truncation

? = one additional letter

ti,ab,hw,de = terms in either title, abstract, heading word, or descriptor fields

adj3 = terms within three words of each other (any order).

Appendix 5. CINAHL strategy

Cumulative Index to Nursing and Allied Health Literature (CINAHL Complete)

via EBSCO Host http://web.b.ebscohost.com/

Date range: Inception – 6th January 2023

Date searched: 6th January 2023

Records retrieved: 1406

S47 S21 AND S46 (1,406)

S46 S37 OR S45 (1,639,735)

S45 S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 (1,294,096)

S44 TI before N3 after OR AB before N3 after (95,991)

S43 (MH "Controlled Before-After Studies") (232)

S42 (multicentre* or multi-centre* or multicenter* or multi-center*) OR AB (multicentre* or multi-centre* or multicenter* or multi-center*) (393,726)

S41 (MH "Multicenter Studies") (356,008)

S40 TI assign* OR AB assign* (93,757)

S39 TI (group or groups) OR AB (group or groups) (936,230)

S38 (MH "Control Group") (13,464)

S37 S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 (999,131)

S36 AB (cluster W3 RCT) (482)

S35 (crossover design) OR MH (comparative studies) (475,262)

S34 AB (control W5 group) (141,387)

S33 PT (randomized controlled trial) (149,463)

S32 MH (placebos) (13,922)

S31 MH (sample size) AND AB (assigned OR allocated OR control) (4,430)

S30 TI trial (174,514)

S29 AB random* (391,367)

S28 TI randomised OR randomized (315,756)

S27 MH "Cluster Sample" (5,174)

S26 MH "Pretest-Posttest Design" (51,569)

S25 MH "Random Assignment" (77,379)

S24 MH "Single-Blind Studies" (15,866)

S23 MH "Double-Blind Studies" (54,052)

S22 MH "Randomized Controlled Trials" (136,225)

S21 S13 AND S20 (3,118)

S20 S14 OR S15 OR S16 OR S17 OR S18 OR S19 (19,499)

S19 TI ((PAP or PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong#)) OR AB ((PAP or PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong#)) (2,115)

S18 TI ((((continuous* or positive or airway* or air-way*) N3 pressure*) or positive-pressure*) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong#)) OR AB ((((continuous* or positive or airway* or air-way*) N3 pressure*) or positive-pressure*) and (source* or device* or interface* or driver* or operator* or generator* or machine* or mask* or face-mask* or headgear* or head gear or head-gear or headbox or head box or head-box or helmet* or bag* or BVM or AMBU or "Infant Flow" or mouthpiece* or mouth piece* or mouth-piece* or nebuli?er* or prong#)) (2,767)

S17 TI ((PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (airway* or air-way* or breath# or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)) OR AB ((PPV or CPAP or C-PAP or NCPAP or BiPAP or APRV or IPPB or IPPV) and (airway* or air-way* or breath# or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)) (3,825)

S16 TI (((airway* or air-way*) N3 pressure*) and (breath# or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)) OR AB (((airway* or air-way*) N3 pressure*) and (breath# or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)) (4,614)

S15 TI ((((continuous* or positive) N3 pressure*) or (positive-pressure* or PAP)) and (airway* or air-way* or breath# OR or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)) OR AB ((((continuous* or positive) N3 pressure*) or (positive-pressure* or PAP)) and (airway* or air-way* or breath# OR or breathing or ventilat* or respir* or inspir* or inhal* or expir* or exhal*)) (10,021)

S14 MH "Positive Pressure Ventilation+" (12,707)

S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 (304,732)

S12 TI (baby or babies) OR AB (baby or babies) (38,651)

S11 TI infan* OR AB infan* (133,167)

S10 TI (LBW or VLBW or ELBW) OR AB (LBW or VLBW or ELBW) (3,979)

S9 TI low-birthweight* OR AB low-birthweight* (3,186)

S8 TI (low N3 (birthweight* or birth weight* or birth-weight*)) OR AB (low N3 (birthweight* or birth weight* or birth-weight*)) (14,338)

S7 TI (prematur* N3 (birth* or born or deliver*)) OR AB (prematur* N3 (birth* or born or deliver*)) (5,547)

S6 TI (preemie* or premie or premies) OR AB (preemie* or premie or premies) (363)

S5 TI (preterm or preterms or pre term or pre terms or pre-term or pre-terms) OR AB (preterm or preterms or pre term or pre terms or pre-term or pre-terms) (41,148)

S4 TI (newborn* or new born* or new-born* or newly born* or newly-born*) OR AB (newborn* or new born* or new-born* or newly born* or newly-born*) (38,153)

S3 TI (neonat* or neo nat* or neo-nat*) OR AB (neonat* or neo nat* or neo-nat*) (81,066)

S2 MH "Childbirth, Premature" (13,094)

S1 MH "Infant, Newborn+" (158,726)

Key:

MH + = exploded indexing term (MeSH)

MH = indexing term (MeSH)

* = truncation

= up to one additional letter

? = one replacement letter

TI = terms in the title

AB = terms in the abstract

N3 = terms near three words of each other (any order).

W5 = terms within three words of each other (specified order).

Appendix 6. Trial registry strategies

ClinicalTrials.gov

via https://clinicaltrials.gov/

Date searched: 6th January 2023

Records retrieved: 653

Other Terms: (infan* OR baby OR neonat* OR prematur* OR newborn* OR LBW OR VLBW OR ELBW) AND ((PAP OR PPV OR (positive AND pressure)) AND (airway* OR breathing OR ventilat* OR respir*))

International Clinical Trials Registry Platform (ICTRP)

via https://trialsearch.who.int/

Date searched: 6th January 2023

Records retrieved: 212 records for 211 trials

Advanced Search:

Intervention: ((PAP OR PPV OR (positive AND pressure)) AND (airway OR breathing OR ventilation OR respiration))

Recruitment Status: All

Search for Clinical Trials in Children

Appendix 7. Risk of bias tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality (to meet the validity criteria) of the trials. For each trial, we sought information regarding the method of randomisation and the blinding and reporting of all outcomes of all the infants enrolled in the trial. We assessed each criterion as low, high, or unclear risk. Two review authors separately assessed each study. Any disagreements were resolved by discussion. We added this information to Characteristics of included studies. We evaluated the following issues and entered the findings into the risk of bias table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

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

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

c. unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

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

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

c. unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from the knowledge of which intervention a participant had received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

a. low risk, high risk, or unclear risk for participants;

b. low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

a. low risk for outcome assessors;

b. high risk for outcome assessors; or

c. unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions had been 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. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

a. low risk (< 20% missing data);

b. high risk (≥ 20% missing data); or

c. unclear risk.

6. Selective reporting bias. Are reports of the study free of the suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

a. low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);

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

c. unclear risk.

7. Other sources of bias. Did the study appear to be free of other problems that could put it at high risk of 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:

a. low risk;

b. high risk; or

c. unclear risk

We explored the impact of the level of bias through undertaking sensitivity analyses as needed.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the development and completion of this review.

DECLARATIONS OF INTEREST

RP has no interests to declare.

ADP has no interests to declare.

PD has no interests to declare.

SO has no interests to declare.

WM is Co-coordinating Editor of Cochrane Neonatal but was not involved in the editorial acceptance or processes for this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review focuses on a subtopic of an earlier protocol and review (De Paoli 2002; De Paoli 2008). We made the following changes to the review at the request of the World Health Organization (WHO).

- Updating of Background section.
- Modification of both primary and secondary outcome measures in consultation with authorship team and WHO.
- Modification of selected subgroup analyses in consultation with authorship team and WHO.
- Addition of risk of bias assessment.
- Addition of GRADE assessment and summary of findings tables.

An Information Specialist wrote new search strategies which were run without date limits.

We prespecified that infants should receive 'nasal CPAP'. We included one trial in which both intervention and control arms received "nasopharyngeal CPAP" (Bahman-Bijari 2011).