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[Intervention Review]

Continuous distending pressure for respiratory distress in preterm infants

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ABSTRACT

Background

Respiratory distress syndrome (RDS) is the single most important cause of morbidity and mortality in preterm infants. In infants with progressive respiratory insufficiency, intermittent positive pressure ventilation (IPPV) with surfactant is the standard treatment for the condition, but it is invasive, potentially resulting in airway and lung injury. Continuous distending pressure (CDP) has been used for the prevention and treatment of RDS, as well as for the prevention of apnoea, and in weaning from IPPV. Its use in the treatment of RDS might reduce the need for IPPV and its sequelae.

Objectives

To determine the effect of continuous distending pressure (CDP) on the need for IPPV and associated morbidity in spontaneously breathing preterm infants with respiratory distress.

Subgroup analyses were planned on the basis of birth weight (> or < 1000 or 1500 g), gestational age (groups divided at about 28 weeks and 32 weeks), methods of application of CDP (i.e. CPAP and CNP), application early versus late in the course of respiratory distress and high versus low pressure CDP and application of CDP in tertiary compared with non-tertiary hospitals, with the need for sensitivity analysis determined by trial quality.

At the 2008 update, the objectives were modified to include preterm infants with respiratory failure.

Search methods

We used the standard search strategy of the Neonatal Review Group. This included searches of the Oxford Database of Perinatal Trials, the Cochrane Central Register of Controlled Trials (CENTRAL, 2015 Issue 4), MEDLINE (1966 to 30 April 2015) and EMBASE (1980 to 30 April 2015) with no language restriction, as well as controlled-trials.com, clinicaltrials.gov and the International Clinical Trials Registry Platform of the World Health Organization (WHO).

Selection criteria

All random or quasi-random trials of preterm infants with respiratory distress were eligible. Interventions were continuous distending pressure including continuous positive airway pressure (CPAP) by mask, nasal prong, nasopharyngeal tube or endotracheal tube, or continuous negative pressure (CNP) via a chamber enclosing the thorax and the lower body, compared with spontaneous breathing with oxygen added as necessary.

Data collection and analysis

We used standard methods of The Cochrane Collaboration and its Neonatal Review Group, including independent assessment of trial quality and extraction of data by each review author.

Main results

We included six studies involving 355 infants - two using face mask CPAP, two CNP, one nasal CPAP and one both CNP (for less ill babies) and endotracheal CPAP (for sicker babies). For this update, we included no new trials.

Continuous distending pressure (CDP) is associated with lower risk of treatment failure (death or use of assisted ventilation) (typical risk ratio (RR) 0.65, 95% confidence interval (CI) 0.52 to 0.81; typical risk difference (RD) -0.20, 95% CI -0.29 to -0.10; number needed to treat for an additional beneficial outcome (NNTB) 5, 95% CI 4 to 10; six studies; 355 infants), lower overall mortality (typical RR 0.52, 95% CI 0.32 to 0.87; typical RD -0.15, 95% CI -0.26 to -0.04; NNTB 7, 95% CI 4 to 25; six studies; 355 infants) and lower mortality in infants with birth weight above 1500 g (typical RR 0.24, 95% CI 0.07 to 0.84; typical RD -0.28, 95% CI -0.48 to -0.08; NNTB 4, 95% CI 2.00 to 13.00; two studies; 60 infants). Use of CDP is associated with increased risk of pneumothorax (typical RR 2.64, 95% CI 1.39 to 5.04; typical RD 0.10, 95% CI 0.04 to 0.17; number needed to treat for an additional harmful outcome (NNTH) 17, 95% CI 17.00 to 25.00; six studies; 355 infants). We found no difference in bronchopulmonary dysplasia (BPD), defined as oxygen dependency at 28 days (three studies, 260 infants), as well as no difference in outcome at nine to 14 years (one study, 37 infants).

Authors' conclusions

In preterm infants with respiratory distress, the application of CDP as CPAP or CNP is associated with reduced respiratory failure and mortality and an increased rate of pneumothorax. Four out of six of these trials were done in the 1970s. Therefore, the applicability of these results to current practice is difficult to assess. Further research is required to determine the best mode of administration.

PLAIN LANGUAGE SUMMARY

Continuous distending pressure for respiratory distress in preterm infants

Review question: In spontaneously breathing preterm infants with respiratory failure, does continuous distending pressure (CDP) of the lung reduce the need for assisted ventilation and other associated complications of prematurity?

Background: Respiratory distress syndrome (RDS) is the most common cause of disease and death in babies born before 34 weeks' gestation. Intermittent positive pressure ventilation (IPPV) has been the standard way of helping these babies breathe. A simpler method of assisting breathing is to provide continuous distending pressure of the lung, either as continuous positive pressure to the airway or as continuous negative pressure (partial vacuum).

Search dates: The search was conducted in April 2015.

Study characteristics: Six studies of moderate quality were identified for inclusion.

The source of distending pressure was a negative pressure chamber in two studies, face mask continuous positive airway pressure (CPAP) in two studies, nasal CPAP in one study and negative pressure for less severe illness and endotracheal CPAP when more severe in another study. The studies were small, and four of the six were conducted before surfactant therapy was available.

Key results: The review of trials found that outcomes for babies were improved. Fewer required IPPV and fewer died, and with these two outcomes combined, fewer babies died or required IPPV. It was also found that CDP can increase the rate of pneumothorax (air outside the lung within the chest cavity).

Conclusion: Some meaningful benefits were found when continuous distending pressure (CDP) was used for respiratory distress syndrome in preterm babies.

BACKGROUND

Description of the condition

Respiratory failure due to pulmonary disease, particularly respiratory distress syndrome (RDS), is the most important cause of morbidity and mortality in preterm infants (Bancalari 1992; Greenough 2004). Most causes of respiratory distress present in a similar manner, sometimes making precise diagnosis difficult. Intermittent positive pressure ventilation (IPPV) with surfactant treatment is the standard treatment for the condition. The major difficulty with IPPV is that it is invasive and contributes to airway and lung injury, including the development of bronchopulmonary dysplasia. Surfactant has brought some amelioration to this problem (Soll 2004).

Description of the intervention

Therapy for respiratory distress traditionally consisted of oxygen given via headbox, low-flow nasal prong or cannula or face mask. Infants with severe disease received IPPV. Continuous distending pressure (CDP) has been used for the prevention and treatment of RDS, as well as for the prevention of apnoea, and in weaning from IPPV. Its use in the treatment of RDS might reduce the need for IPPV and hence its sequelae. Cost saving could occur if more expensive forms of treatment such as IPPV and use of surfactant were avoided.

CDP has been applied as continuous positive airway pressure (CPAP) or as continuous negative pressure (CNP). CPAP is applied via face mask, nasal mask, nasopharyngeal tube or nasal prongs, using a conventional ventilator, bubble circuit or CPAP driver. CNP is applied externally to the thorax using a negative pressure chamber with the seal around the neck; it produces lung distension as a result of negative intrathoracic pressure.

How the intervention might work

Application of positive compared with negative pressure might have different results in terms of effectiveness and complications. As use of CDP depends on the spontaneous respiratory efforts of the infant, those of very low birth weight, who would be expected to have reduced efforts and be more prone to apnoea, might not respond as well.

Why it is important to do this review

Several systematic reviews have examined the effects of CDP, particularly when given as CPAP. Subramaniam 2005 looked at prophylactic CPAP applied to preterm infants immediately after birth, Davis 2004 studied the effects of CPAP on infants immediately after extubation from IPPV and the De Paoli 2008 review looked at devices and pressure sources for applying CPAP. Ho 2004 examined the timing of initiation of CDP in preterm infants with respiratory distress.

A formal evaluation of the use of CDP is required to assess its role in preterm infants with established respiratory distress and to determine which methods of application are appropriate.

A systematic review on this subject has already been published (Bancalari 1992).

OBJECTIVES

To determine the effect of CDP on the need for IPPV and associated morbidity in spontaneously breathing preterm infants with respiratory distress.

Subgroup analyses were planned on the basis of birth weight (> or < 1000 or 1500 g), gestational age (groups divided at about 28 weeks and 32 weeks), methods of application of CDP (i.e. CPAP and CNP), application early versus late in the course of respiratory distress and high versus low pressure CDP and application of CDP in tertiary compared with non-tertiary hospitals, with the need for sensitivity analysis determined by trial quality.

At the 2008 update, the objectives were modified to include preterm infants with respiratory failure.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised studies.

Types of participants

Preterm infants with respiratory failure.

Types of interventions

Continuous distending pressure (CDP) including continuous positive airway pressure (CPAP) by mask, nasal prong, nasopharyngeal tube or endotracheal tube, or continuous negative pressure (CNP) via a chamber enclosing the thorax and the lower body in spontaneously breathing infants, compared with spontaneous breathing with the addition of oxygen if necessary, delivered by means such as mask, headbox or low-flow nasal cannula. We excluded infants receiving IPPV beyond the initial resuscitation period.

Types of outcome measures

Primary outcomes

1. Treatment failure (death or respiratory failure as measured by use of any additional assisted ventilation, blood gas criteria or transfer to a neonatal intensive care unit).
2. Use of assisted ventilation.
3. Respiratory failure by blood gas criteria.
4. Transfer to a neonatal intensive care.
5. Mortality at 28 days and at hospital discharge.

At the 2008 update of the review, review authors modified the definition of treatment failure and added the two additional outcomes of transfer to a neonatal intensive care unit and respiratory failure by blood gas criteria.

Secondary outcomes

1. Pulmonary morbidity as judged by pulmonary air leak (any air leak, gross air leak including pneumothorax), duration of oxygen therapy, bronchopulmonary dysplasia (BPD) (respiratory support and/or oxygen therapy at 28 days' and at 36 weeks' postmenstrual age).
2. Use of surfactant.

3. Other morbidities such as intraventricular haemorrhage, cystic brain lesions on ultrasound, retinopathy of prematurity, necrotising enterocolitis and duration of hospital stay.
4. Neurodevelopment in childhood (death or severe disability (as defined by authors), severe disability, any disability, cerebral palsy).

At the 2009 update, review authors defined prespecified neurodevelopmental outcomes in childhood.

Search methods for identification of studies

We used the standard search strategy of the Neonatal Review Group ([Appendix 1](#)). This included searches of the Oxford Database of Perinatal Trials, the Cochrane Central Register of Controlled Trials (CENTRAL, 2015 Issue 4) and previous reviews including cross-references, abstracts, conference and symposia proceedings, expert informants and journal handsearching. We searched MEDLINE (1966 to 30 April 2015), EMBASE (1980 to 30 April 2015) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) to 30 April 2015 using the following terms: respiratory distress syndrome, hyaline membrane disease, continuous distending airway pressure, continuous positive airway pressure, continuous positive transpulmonary pressure, continuous transpulmonary pressure, continuous inflating pressure, continuous negative distending pressure, continuous negative pressure or continuous airway pressure.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group.

Selection of studies

We included all randomised and quasi-randomised controlled trials fulfilling the selection criteria described in the previous section. Review authors reviewed the results of the search and separately selected studies for inclusion. We resolved disagreements by discussion.

Data extraction and management

Two review authors separately extracted, assessed and coded all data for each study. We replaced any standard error of the mean with the corresponding standard deviation and resolved disagreements by discussion. For each study, one review author entered final data into RevMan and a second review author checked the data.

We performed statistical analyses using Review Manager (RevMan) software and analysed categorical data using risk ratio (RR), risk difference (RD) and the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH). We analysed continuous data using mean difference (MD). We reported the 95% confidence interval (CI) on all estimates and used a fixed-effect model for meta-analysis.

Assessment of risk of bias in included studies

We employed the standard methods of the Cochrane Neonatal Review Group and assessed the methodological quality of the studies according to recommendations provided in [Higgins 2011](#), using the following key criteria: allocation concealment (blinding of

randomisation), blinding of intervention, completeness of follow-up and blinding of outcome measurement/assessment. For each criterion, we rated assessment as low risk, high risk or unsure risk (cannot tell). Two review authors separately assessed each study and resolved disagreements by discussion.

Measures of treatment effect

We presented dichotomous data as a typical risk ratio with 95% confidence intervals, and continuous data as mean difference with 95% confidence intervals.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the I^2 statistic. We regarded heterogeneity as probably not important if less than 40%, moderate if between 40% and 60% and substantial if I^2 was greater than 60% ([Deeks 2011](#)).

Data synthesis

We carried out statistical analysis using Review Manager software ([RevMan 2011](#)). We used fixed-effect meta-analysis for combining data when it was reasonable to assume that studies were examining the same intervention and we determined that trial populations and methods used were similar.

Subgroup analysis and investigation of heterogeneity

We examined the treatment effects of individual trials and heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. If we detected statistical heterogeneity, we explored possible causes (e.g. differences in study quality, participants, intervention regimens or outcome assessments) using post hoc subgroup analyses.

We performed specific subgroup analyses as described in the [Objectives](#) section of this review.

RESULTS

Description of studies

Results of the search

In the 2008 update, one new trial was identified ([Buckmaster 2007](#)) and two were excluded. In 2009, three new trials were identified and all were excluded ([Colnaghi 2008](#); [Morley 2008](#); [Rojas 2009](#)). In the 2015 update, we identified another four trials, which we excluded ([Dunn 2011](#); [Finer 2010](#); [Sandri 2010](#); [Tapia 2012](#)). We listed reasons for exclusion in the [Characteristics of excluded studies](#).

Included studies

We included six studies ([Belenky 1976](#); [Buckmaster 2007](#); [Durbin 1976](#); [Fanaroff 1973](#); [Rhodes 1973](#); [Samuels 1996](#)) and provided details of these studies in the [Characteristics of included studies](#). Entry criteria for participants were based on a clinical diagnosis of respiratory failure and spontaneous breathing at an FiO_2 that ranged from 0.3 to 0.95. In [Samuels 1996](#), included infants had respiratory distress not due to infection, meconium aspiration or congenital heart disease, and all were in respiratory failure thought to be due to RDS but without radiological confirmation. The study population was randomly assigned within strata that were formed according to gestation and whether intubated or

not. We included in this review only preterm infants breathing spontaneously at trial entry; study authors supplied individual patient data on this group of participants. [Buckmaster 2007](#) included neonates with respiratory distress not due to cardiac disease. Study authors supplied data for preterm infants. All of these infants had respiratory failure thought to be due to RDS, but it is not possible to exclude other conditions, in particular, meconium aspiration in eight infants with meconium-stained amniotic fluid. The study was performed at non-tertiary hospitals.

Antenatal steroids were administered to less than 20% of participants in [Samuels 1996](#) and 35% in [Buckmaster 2007](#). The other studies did not mention rates of antenatal steroid exposure. [Samuels 1996](#) was the only trial in which surfactant use was reported. Some of the participants in [Buckmaster 2007](#) may have received surfactant after transfer to a neonatal intensive care unit, but this was not recorded.

The source of distending pressure was a negative pressure chamber in two studies ([Fanaroff 1973](#); [Samuels 1996](#)), face mask CPAP in two studies ([Belenky 1976](#); [Rhodes 1973](#)) and nasal CPAP in one study ([Buckmaster 2007](#)). The other study used negative pressure for less severe illness and endotracheal CPAP when more severe ([Durbin 1976](#));

Two studies performed a subgroup analysis of mortality for very low birth weight infants ([Belenky 1976](#); [Rhodes 1973](#)). [Buckmaster 2007](#) stratified for gestations of 31 to 33 weeks and 34 to 36 weeks.

The study by [Belenky 1976](#) included both spontaneously breathing infants on face mask CPAP and ventilated infants on face mask or endotracheal IPPV with PEEP. Only infants who were spontaneously breathing at trial entry were eligible for this review. The published report of this study describes in infants spontaneously breathing at trial entry only subsequent use of IPPV; we obtained from the study author information on other outcomes in such infants.

In one study, neurodevelopmental assessment was done at 9 to 15 years of age ([Samuels 1996](#)).

Excluded studies

We excluded 10 studies and provided details under [Characteristics of excluded studies](#). One study ([Tooley 2003](#)) included infants of 25 to 28 weeks' gestation who were intubated at birth, given a single dose of surfactant, then randomly assigned at about one hour of age to extubation, to nasal CPAP or to continued conventional IPPV. No criteria for the diagnosis of RDS were given. The second study

([Swyer 1973](#)) was a randomised comparison of three continuous distending pressure methods, but no control (supportive care) treatment group was included. The Pieper study was performed in a developing country. Participants were extremely low birth weight babies 750 to 1000 g or 26 to 28 weeks' gestation who had no access to intensive care. This study was not randomised ([Pieper 2003](#)). We excluded one study ([Colnaghi 2008](#)) because no clinical outcomes were measured. [Morley 2008](#) randomly assigned preterm infants at 25 to 28 weeks' gestation with respiratory distress at five minutes of age to nasal CPAP or mechanical ventilation. No control group was allocated to supportive care. One study ([Rojas 2009](#)) included infants born from 27 to 31 weeks' gestation who had respiratory distress within the first hour of life randomly assigned to receive surfactant followed by nasal CPAP or nasal CPAP alone. No control group was treated with supportive care. [Dunn 2011](#) examined three interventions - prophylactic surfactant, intubation-surfactant-extubation and nasal CPAP - for preterm infants at 26 to 29 weeks' immediately after birth. [Sandri 2010](#) randomly assigned infants to prophylactic surfactant and nasal CPAP or nasal CPAP alone immediately after birth, whereas in another trial ([Finer 2010](#)), infants received CPAP alone or surfactant and mechanical ventilation as a prophylactic strategy. One further study ([Tapia 2012](#)) examined prophylactic CPAP compared with supportive care, which included headbox or low flow nasal cannula oxygen when indicated.

Risk of bias in included studies

We provided details of the risk of bias for each study in the [Characteristics of included studies](#) section. A graphical summary of our judgements is shown in [Figure 1](#) and [Figure 2](#). Five of the six studies used random allocation ([Belenky 1976](#); [Buckmaster 2007](#); [Durbin 1976](#); [Fanaroff 1973](#); [Samuels 1996](#)), one used off-site computer-generated random sequence and allocation ([Buckmaster 2007](#)), three used sealed envelopes ([Durbin 1976](#); [Fanaroff 1973](#); [Samuels 1996](#)) and three did not mention the method of generation of a random sequence. One study ([Rhodes 1973](#)) used alternate allocation. Blinding of treatment or outcome assessment was not feasible. Three studies ([Buckmaster 2007](#); [Durbin 1976](#); [Samuels 1996](#)) stated how many were randomly assigned. In all three studies, more than 90% were analysed. Three studies ([Belenky 1976](#); [Fanaroff 1973](#); [Rhodes 1973](#)) stated only the numbers analysed, and it is not possible to tell how many exclusions were made after randomisation. Outcome data for the only study that included outcomes in childhood were available for 71% of the included preterms ([Samuels 1996](#)).

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Intervention	Blinding (performance bias and detection bias): Short term outcomes	Blinding (performance bias and detection bias): Childhood outcomes	Incomplete outcome data (attrition bias): Short term outcomes	Incomplete outcome data (attrition bias): Childhood outcomes	Selective reporting (reporting bias)	Other bias
Belenky 1976	+	?	-	-		?		?	?
Buckmaster 2007	+	+	-	-		+		+	?
Durbin 1976	?	+	-	-		+		?	?
Fanaroff 1973	?	+	-	-		?		?	?
Rhodes 1973	-	-	-	-		?		?	?
Samuels 1996	?	+	-	-	+	+	?	+	?

Effects of interventions

Six trials (Belenky 1976; Buckmaster 2007; Durbin 1976; Fanaroff 1973; Rhodes 1973; Samuels 1996), which included a total of 355 infants, met eligibility criteria.

Continuous distending pressure vs standard care (Comparison 1)

Treatment failure (death or respiratory failure measured by use of additional ventilation, blood gas criteria or transfer to a NICU) (Outcome 1.1)

All trials reported treatment failure as death or respiratory failure defined by the need for additional ventilation, one trial measured treatment failure as death or respiratory failure by blood gas criteria (Buckmaster 2007) and one trial as death or transfer to a neonatal intensive care unit (NICU) (Buckmaster 2007). In three trials (Buckmaster 2007; Fanaroff 1973; Rhodes 1973), failure defined by use of mechanical ventilation was significantly reduced in the CDP group. The meta-analysis of all six trials supports a significant reduction in treatment failure in the CDP group compared with the control group (typical RR 0.65, 95% CI 0.52 to 0.81; typical RD -0.20, 95% CI -0.29 to -0.10; NNTB 5, 95% CI 4 to 10; $I^2 = 46\%$). Treatment failure defined by blood gas criteria was significantly reduced in the one trial that measured this (RR 0.53, 95% CI 0.32 to 0.90; RD -0.18, 95% CI -0.32 to -0.04; NNTB 6, 95% CI 4 to 25). Treatment failure defined by transfer to a NICU was significantly reduced in the only trial that measured this (RR 0.49, 95% CI 0.30 to 0.78; RD -0.24; 95% CI -0.38 to -0.10; NNTB 5, 95% CI 3 to 10), (Buckmaster 2007).

Death or respiratory failure by blood gas criteria (Outcome 1.1.2)

Respiratory failure by blood gas criteria was significantly reduced in the only study reporting this outcome (Buckmaster 2007) (RR 0.53, 95% CI 0.32 to 0.90; RD -0.18, 95% CI -0.32 to -0.04; NNTB 6, 95% CI 4 to 25).

Use of additional ventilatory assistance (Outcome 1.2)

One trial (Buckmaster 2007) showed a difference with the use of IPPV, and four trials did not (Belenky 1976; Durbin 1976; Fanaroff 1973; Samuels 1996). The meta-analysis showed reduced use of IPPV in the CDP group (RR 0.72, 95% CI 0.56 to 0.91; RD -0.15, 95% CI -0.25 to -0.05; NNTB 7, 95% CI 5 to 22; 314 infants; $I^2 = 14\%$).

Transfer to a NICU (Outcome 1.3)

Buckmaster reported transfer to a NICU. This was significantly reduced in the CDP group (RR 0.49, 95% CI 0.30 to 0.78; RD -0.24, 95% CI -0.38 to -0.10; NNTB 5, 95% CI 3 to 10).

Mortality (Outcomes 1.4 to 1.6)

Six trials reported effects on mortality, but only Belenky 1976 found a significant reduction (RR 0.38, 95% CI 0.14 to 0.99). The meta-analysis of all six trials supports a reduction in mortality (typical RR 0.52, 95% CI 0.32 to 0.87; typical RD -0.15, 95% CI -0.26 to -0.04; NNTB 7, 95% CI 4 to 25; 355 infants; $I^2 = 0\%$). Two trials (Belenky 1976; Rhodes 1973) reported mortality by birth weight less than or greater than 1500 g. For infants over 1500 g, birth weight mortality was reduced in the CDP group (typical RR 0.24, 95% CI 0.07 to 0.84; typical RD -0.28, 95% CI -0.48 to -0.08; NNTB 4, 95% CI 2 to 13; 60 infants; $I^2 = 0\%$). For the 32 infants in the two trials with birth weight of 1500 g or less, no difference was found.

Pulmonary morbidity (Outcomes 1.7 to 1.9 and Outcome 1.11)

Six trials reported the rate of pneumothorax at any time. Although no individual trial showed a significant increase, overall an increase

was found in the CDP group (typical RR 2.64, 95% CI 1.39 to 5.04; typical RD 0.10, 95% CI 0.04 to 0.17; NNTB 10, 95% CI 6 to 25; $I^2 = 0\%$; 355 participants). Six trials reported the presence of pneumothorax after trial entry, and overall a similar increase was noted in the CDP group (typical RR 2.42, 95% CI 1.26 to 4.65; typical RD 0.09, 95% CI 0.03 to 0.15; NNTB 11, 95% CI 7 to 33; $I^2 = 0\%$; 351 infants). No evidence showed differences between treatment and control groups in the duration of oxygen therapy (two trials, 76 infants; Durbin 1976; Samuels 1996) or in rates of BPD at 28 days (three trials, 260 infants; Belenky 1976; Buckmaster 2007; Samuels 1996). 'Minimal bronchopulmonary dysplasia' (not defined) at discharge among survivors was reported in one trial (Fanaroff 1973) (0/11 in the CDP group and 2/8 in the control group).

Use of surfactant (Outcome 1.10)

One trial (Samuels 1996) reported that fewer infants received surfactant in the CNP group (3/26) than in the control group (7/26), but this difference was not significant.

Intraventricular haemorrhage and cystic brain lesions

One trial (Samuels 1996) reported outcomes for parenchymal haemorrhage and periventricular leucomalacia or cysts. No cases were found in either group.

Necrotising enterocolitis

One trial (Samuels 1996) reported necrotising enterocolitis. No cases were found in either group.

Retinopathy of prematurity

Fanaroff 1973 reported retrolental fibroplasia among survivors and found only one case with mild proliferative changes in the control group. Samuels 1996 reported retinopathy of prematurity and found grade I changes in two of 15 babies examined in the CNP group and in one of 13 babies examined in the control group.

Neurodevelopment in childhood (Outcomes 1.11 to 1.19)

Only one study reported long-term follow-up (Samuels 1996). Mortality outcomes were available for 30 of the 52 included infants, and disability outcomes for 37. No difference was found in the combined outcome of severe disability or death (four out of 19 vs three of 18), any disability (seven out of 18 vs 12 of 19) or cerebral palsy (two in the CNP group and none in the control group). Subgroup analysis by gestation showed no differences.

Subgroup analyses

Subgroup analyses by type and by early use of CDP (CPAP or CNP) resulted in small numbers in the meta-analyses and, allowing for this, the results are not substantially different from the overall analysis (Comparisons 2 to 6). The reduction in failure rate in the CDP group reached statistical significance in both CNP (typical RR 0.61, 95% CI 0.41 to 0.90) and CPAP (typical RR 0.61, 95% CI 0.45 to 0.81) subgroups.

Sensitivity analyses, which excluded the study using quasi-random patient allocation (Rhodes 1973) and the study whose only infants eligible for inclusion in this review were those who were breathing spontaneously at trial entry (Belenky 1976), did not yield substantially different results.

DISCUSSION

Summary of main results

We found that CDP compared with supportive care reduces treatment failure, whether it is defined by the combined outcome of mortality with the need for IPPV, deterioration of blood gas parameters or need for admission to a NICU. Similar reductions in treatment failure were seen in subgroup analyses of trials using CPAP and CNP. We found that CDP reduces mortality as well as the need for additional ventilatory support. An increase was found in any pneumothorax and pneumothorax appearing after the start of the intervention. Data on other adverse events such as bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia and necrotising enterocolitis are insufficient. Data on long-term neurodevelopmental outcomes are also insufficient. Data that are available suggest that CDP does not have an adverse effect on neurodevelopmental outcomes in childhood.

Overall completeness and applicability of evidence

For several reasons, the results of this review, which included trials carried out in the 1970s, have limited application to current neonatal care. In the 1970s, antenatal corticosteroid use was uncommon and surfactant treatment was not available. The mean birth weight of participants in the studies reviewed was between 1700 and 2000 g, with three trials ([Belenky 1976](#); [Durbin 1976](#); [Fanaroff 1973](#)) excluding infants weighing less than 1000 g. CPAP was applied by face mask in two of the three trials of CPAP ([Belenky 1976](#); [Rhodes 1973](#)), and this route has been reported to be associated with adverse effects ([Pape 1976](#)). Currently, the nasal route is the standard way of delivering CPAP ([Davis 2004](#)), and differences in efficacy have been shown between devices delivering nasal CPAP ([De Paoli 2008](#)). The intervention in early trials was initiated later than would be current practice ([Morley 2008](#); [Narendran 2003](#); [Tooley 2003](#)), with mean age at entry greater than 10 hours in four studies and 28 hours in the fifth. [Buckmaster 2007](#) initiated CPAP at a mean of three hours. Earlier CPAP is more effective in preventing intubation for IPPV than later CPAP in infants with RDS ([Ho 2004](#)). Five of the six trials provided outcomes only up to discharge from the neonatal unit. Only one study provided information on outcomes in childhood, so data on adverse neurological outcomes are extremely limited.

This review is historically important because it establishes the role of CDP in preterm infants with respiratory distress. In addition, the results are currently relevant in settings where access to intensive care is not immediately available, such as in Level 2 hospitals or in low and middle income settings where intensive care is limited. However, conditions today in low and middle income countries have certain dissimilarities to those of the studies from the 1970s included in this review. Today's settings have some availability, even if limited, of antenatal steroids, surfactant and ventilators. CDP is an inexpensive therapy; therefore randomised trials in developing countries where resources are scarce seem appropriate. However, the reduced mortality seen in our meta-analysis makes randomisation to headbox oxygen or other forms of oxygen therapy (compared with CDP) difficult. This problem is well illustrated by the trial of Pieper et al ([Pieper 2003](#)). Loss of equipoise by the clinical staff at participating South African centres led to cessation of randomisation and allocation of infants to CPAP on the basis of availability of this form of care.

Quality of the evidence

These data should be interpreted with caution as in the studies reviewed, the numbers of infants were small, blinding of treatment was not possible and blinding of the outcome assessment was reported in only one study for the outcomes in childhood, thus possibly introducing bias.

Potential biases in the review process

We found moderate heterogeneity for our primary outcome ($I^2 = 46\%$). However, the results did not change substantially and remained significant with random-effects meta-analysis. Inclusion of the subgroup of spontaneously breathing infants from the [Belenky 1976](#) trial could be criticised, as group allocation to CDP or control was not stratified by this characteristic, and this could lead to imbalance. That imbalance is present is suggested by the greater birth weight of the group allocated to CPAP. Removal of this trial as part of a sensitivity analysis did not substantially alter the results.

AUTHORS' CONCLUSIONS

Implications for practice

In preterm infants with respiratory distress, the application of CDP as CPAP or CNP is associated with reduced respiratory failure and reduced mortality. CDP is associated with an increased rate of pneumothorax. The applicability of these results to current practice is difficult to assess, given the intensive care setting of the 1970s in which four of these trials were done. The contribution of the two studies done in the post-surfactant era does not alter the overall results. The only study with reported outcomes in childhood suggests no long-term adverse effects of CDP on neurodevelopment. CPAP has a role in nurseries where intensive care is not immediately available, which may include settings such as low income countries with no access to intensive care.

Implications for research

Further trials of CDP (preferably using low cost nasal CPAP) compared with supportive care for preterm infants with RDS could be carried out in low income countries to assess relative benefits and harms in such settings. Such studies should ideally include follow-up into childhood. The comparison group should be representative of supportive care available in the setting, such as oxygen delivered by headbox, low flow nasal cannula or other delivery of oxygen that does not generate pressure. In other settings, further studies are required to evaluate the use of early nasal CPAP with or without prior temporary tracheal intubation for surfactant administration ([Verder 1999](#)). More studies are required to determine the optimum level (pressure) and mode of delivery of CPAP.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Belenky 1976

Methods	Concealment of allocation unclear. Drawing of cards. Not stated whether in envelopes. No blinding of treatment or outcome assessment. Completeness of follow-up not clear
Participants	51 preterm infants (22 CPAP, 29 control) who were spontaneously breathing at trial entry. Clinical and x-ray evidence of RDS, absence of infection and congenital abnormalities. PaO ₂ 50 mmHg or less on FiO ₂ of 0.6. Outborns meeting eligibility criteria for less than 6 hours included. Stratified for weight: 1000 to 1500 g, 1501 to 2000 g, > 2000 g. Infants < 1000 g excluded. Age at trial entry for weight stratified groups between 10 hours (SD = 6) and 17 hours (SD = 13)
Interventions	Face mask CPAP or PEEP (6 to 14 cm water) vs oxygen or IPPV without PEEP. Endotracheal IPPV initiated in those on face mask IPPV with gastric distension or inadequate ventilation
Outcomes	IPPV in group spontaneously breathing at trial entry. Mortality, mortality by weight, pneumothorax, bronchopulmonary dysplasia

Belenky 1976 (Continued)

Notes From a total of 71 trial participants, 20 were excluded on the grounds that they were not spontaneously breathing at trial entry. Additional information was supplied by study authors on the outcomes for 51 included infants. Of these, birth weight in the group allocated to CPAP is significantly higher

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random card selection
Allocation concealment (selection bias)	Unclear risk	'Patients were assigned to ... by drawing cards'
Blinding (performance bias and detection bias) Intervention	High risk	Blinding of the intervention would not be possible
Blinding (performance bias and detection bias) Short term outcomes	High risk	No blinding of treatment or outcome assessment
Incomplete outcome data (attrition bias) Short term outcomes	Unclear risk	Completeness of follow-up not clear
Selective reporting (reporting bias)	Unclear risk	None detected
Other bias	Unclear risk	Exclusion of 20 infants who were not spontaneously breathing at trial entry may have resulted in an imbalance between groups

Buckmaster 2007

Methods	Random sequence generation and allocation concealed using off-site computer. Stratified by gestation of 31 to 33 and 34 to 36 weeks and by hospital. All infants randomly assigned were included in the analysis. 12 infants withdrawn before primary outcome measurement were not excluded from the analysis
Participants	Infants in non-tertiary hospitals ≥ 31 and < 37 weeks weighing > 1200 g, < 24 hours of age with respiratory distress as defined by recession, grunt, nasal flare and/or tachypnoea, who required $> 30\%$ oxygen in a headbox to maintain oxygen saturation levels $\geq 94\%$ for 30 minutes. For multiples, only the first sibling to meet the inclusion criteria was included
Interventions	Nasal CPAP using Hudson prong and bubble delivery circuit compared with headbox oxygen
Outcomes	Treatment failure or transfer to a neonatal intensive care unit. Transfer to a neonatal intensive care unit, pneumothorax
Notes	300 infants were randomly assigned; of these, 158 who were preterms with respiratory distress without cardiac disease were included in this review. Data were supplied by study authors. It is not possible to exclude meconium aspiration as the cause of respiratory distress in 8 infants with reported meconium staining of amniotic fluid. IVH was not reported, as not all infants had a cranial ultrasound examination. Surfactant not used before the time of transfer. Antenatal steroids used for 35% of infants

Buckmaster 2007 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Off-site computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Random sequence generation and allocation concealed using off-site computer. Stratified by gestation of 31 to 33 weeks and 34 to 36 weeks and by hospital
Blinding (performance bias and detection bias) Intervention	High risk	Blinding of the intervention is not possible
Blinding (performance bias and detection bias) Short term outcomes	High risk	No blinding of short-term outcomes
Incomplete outcome data (attrition bias) Short term outcomes	Low risk	All infants randomly assigned were included in the analysis. 12 infants withdrawn before primary outcome measurement were not excluded from the analysis
Selective reporting (reporting bias)	Low risk	Study protocol was available and prespecified outcomes were reported
Other bias	Unclear risk	None detected

Durbin 1976

Methods	Concealment of allocation adequate (sealed envelope). No blinding of treatment or outcome assessment. Completeness of follow-up adequate
Participants	24 infants (12 CNP, 12 control) with severe RDS > 1000 g, PaO ₂ < 60 mmHg in FiO ₂ > 0.95 for 15 minutes. Mean age (hours) for control group 30.3 (SD = 6.1), and for treatment group 28.2 (SD = 3.7)
Interventions	8 to 12 cmH ₂ O CNP for less severe illness and endotracheal CPAP for more severe vs oxygen. IPPV started if PaO ₂ < 35 mmHg
Outcomes	IPPV, mortality, duration of oxygen, duration on FiO ₂ > 0.5 and > 0.6, any pneumothorax, pneumothorax after randomisation
Notes	Infants with pneumothorax before randomisation were excluded from the analysis of pneumothorax after randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Concealment of allocation adequate (sealed envelope)

Durbin 1976 (Continued)

Blinding (performance bias and detection bias) Intervention	High risk	No blinding of intervention
Blinding (performance bias and detection bias) Short term outcomes	High risk	No blinding of outcome assessment
Incomplete outcome data (attrition bias) Short term outcomes	Low risk	Completeness of follow-up adequate.
Selective reporting (reporting bias)	Unclear risk	Insufficient information available
Other bias	Unclear risk	None detected

Fanaroff 1973

Methods	Concealment of allocation adequate (sealed envelope). Sequential analysis. No concealment of treatment or outcome assessment. Completeness of follow-up uncertain
Participants	29 preterm infants (15 CNP, 14 control) > 1000 g, free from congenital abnormality, with RDS with $PO_2 < 60$ mmHg in FiO_2 0.7. Total participants, 19. Infants matched at allocation for age (< 24 and > 24 hours) and weight group (1000 to 1499, 1500 to 1999, > 2000 g)
Interventions	CNP chamber (6 to 14 cm water negative pressure) vs oxygen hood. Study group failures received mechanical ventilation, and control group failures CPAP or mechanical ventilation
Outcomes	Any further respiratory assistance, mortality, BPD, RLF
Notes	Rate of pneumothorax taken from Bancalari 1992 , who obtained information from study authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Concealment of allocation adequate (sealed envelope). Sequential analysis
Blinding (performance bias and detection bias) Intervention	High risk	No concealment of treatment or outcome assessment
Blinding (performance bias and detection bias) Short term outcomes	High risk	No concealment of treatment or outcome assessment
Incomplete outcome data (attrition bias) Short term outcomes	Unclear risk	Completeness of follow-up uncertain

Fanaroff 1973 (Continued)

Selective reporting (reporting bias)	Unclear risk	Insufficient information available to permit a judgement
Other bias	Unclear risk	None detected

Rhodes 1973

Methods	Concealment inadequate. Alternate allocation to treatment or control group by 500 g birth weight groups. No blinding of treatment or outcome assessment. Completeness of follow-up uncertain
Participants	41 preterm infants (22 CPAP, 19 control) with clinical and x-ray features of RDS and $\text{PaO}_2 < 60$ mmHg in FiO_2 0.5, stratified by 500 g birth weight groups from < 1500 g to > 2500 g Mean age (hours) for intervention group 10.1 (SD = 1.8) and 12.4 (SD = 2.0)
Interventions	Tight-fitting mask CPAP (8 to 10 cm water) vs headbox oxygen. CPAP used on control patients failing headbox treatment. Assisted ventilation given for apnoea requiring bag and mask ventilation, $\text{PaO}_2 < 40$ mmHg in FiO_2 1.0 or $\text{PCO}_2 > 80$ mmHg
Outcomes	Mortality, mortality in < 1500 g, mortality in ≥ 1500 g, assisted ventilation, pneumothorax after randomisation, any pneumothorax
Notes	Infants with pneumothorax before randomisation were excluded from the analysis of pneumothorax after randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternate allocation to treatment or control group by 500 g birth weight groups
Allocation concealment (selection bias)	High risk	Concealment inadequate
Blinding (performance bias and detection bias) Intervention	High risk	No blinding of treatment groups
Blinding (performance bias and detection bias) Short term outcomes	High risk	No blinding of outcome assessment
Incomplete outcome data (attrition bias) Short term outcomes	Unclear risk	Completeness of follow-up uncertain
Selective reporting (reporting bias)	Unclear risk	Insufficient information available to permit a judgement
Other bias	Unclear risk	None detected

Samuels 1996

Methods	Concealment of allocation adequate. Sealed envelopes randomly assigned in sequentially matched pairs. Stratified for gestation, oxygen requirement and whether intubated. No blinding of intervention or outcomes. Follow-up complete to discharge. Mortality outcome at 9 to 15 years was known for 38 of the 52 (73%), and neurodevelopmental outcome or death for 37 (71%)
Participants	At 2 centres, 52 preterm infants with respiratory failure not due to infection or congenital heart disease spontaneously breathing at 4 hours in $\text{FiO}_2 \geq 0.4$ to maintain PO_2 above 60 mmHg (subgroup of trial). Mean (SD) gestational age at birth 32.5 (1.8) vs 31.0 (1.9) weeks, range 30 to 36 vs 29 to 36. Prenatal corticosteroids 5/26 vs 4/26; C/S 22/26 vs 23/26; labour 19/26 vs 21/26; maternal hypertension 11/26 vs 10/26; SGA 5/26 vs 7/26; mean (SD) FiO_2 at entry 0.55 (0.1) vs 0.51 (0.09)
Interventions	CNP chamber 4 to 6 cmH_2O vs headbox oxygen
Outcomes	Mortality at 28 days and at discharge, failure (required IPPV), pneumothorax, BPD, parenchymal intracranial haemorrhage, PVL, NEC, ROP. Neurological outcome at 9 to 14 years (severe disability or death, severe disability, moderate-severe disability, any disability, cerebral palsy, quality of life, behavioural outcomes). Neurodevelopmental assessment was carried out at 9 to 15 years and was reported separately by Telford 2006 (Samuels 1996)
Notes	244 participants were randomly assigned. Of these, the 52 who were preterms with respiratory failure and spontaneously breathing at trial entry were included in this review. Individual participant data on these infants were supplied by study authors. Only 17% of the mothers of the 52 infants received prenatal corticosteroids (similar in each group) Neurodevelopmental assessment was carried out at 9 to 15 years and was reported separately by Telford 2006 (Samuels 1996)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Low risk	Concealment of allocation adequate. Sealed envelopes randomly assigned in sequentially matched pairs. Stratified for gestation, oxygen requirement and whether intubated
Blinding (performance bias and detection bias) Intervention	High risk	No blinding of treatment
Blinding (performance bias and detection bias) Short term outcomes	High risk	No blinding of short-term outcomes
Blinding (performance bias and detection bias) Childhood outcomes	Low risk	Quote: 'Both investigators were masked to the neonatal course'
Incomplete outcome data (attrition bias) Short term outcomes	Low risk	Low risk for short-term outcomes. All followed up to discharge from the hospital
Incomplete outcome data (attrition bias) Childhood outcomes	Unclear risk	Death and neurodevelopmental outcome examined at 9 to 15 years of age in 37/52 (71%). Assessed children were similar to non-assessed children for neonatal characteristics, except that assessed children were more likely to receive surfactant

Samuels 1996 (Continued)

Selective reporting (re-reporting bias)	Low risk	Protocol was not available, but all expected outcomes were assessed
Other bias	Unclear risk	None detected

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Colnaghi 2008	Randomised controlled trial of 2 forms of CPAP. No control group for standard treatment. Primary outcome was pharyngeal pressure. No relevant clinical outcomes
Dunn 2011	Randomised controlled trial in preterm infants at birth of 3 interventions applied immediately after birth: (1) Prophylactic surfactant followed by mechanical ventilation, (2) intubation -surfactant-extubation within 30 minutes of surfactant and (3) prophylactic CPAP within 15 minutes of life. Participating infants did not need to have respiratory distress
Finer 2010	Randomised controlled trial 2 × 2 factorial design comparing prophylactic CPAP or intubation and surfactant followed by mechanical ventilation. At the same time, infants were randomly assigned to 1 of 2 target ranges for oxygen saturation. Infants did not need to have respiratory distress to be enrolled in the study
Morley 2008	Randomised controlled trial of preterm infants 25 to 28 weeks with respiratory distress at 5 minutes of age allocated to nasal CPAP or intermittent positive pressure ventilation. Excluded because no control group for standard treatment was included
Pieper 2003	First 4 of 21 babies allocated randomly but remaining babies allocated according to availability of CPAP system. If CPAP system occupied, baby used as a control
Rojas 2009	Randomised controlled trial of preterm infants 27 to 31 weeks with respiratory distress in the delivery room comparing surfactant and nasal CPAP with nasal CPAP alone. No standard treatment control group
Sandri 2010	Randomised controlled trial of early prophylactic surfactant followed by extubation to CPAP compared with early CPAP followed by selective surfactant. Infants did not need to have respiratory distress to participate
Swyer 1973	Randomised comparison of three continuous distending pressure methods, but no control (standard) treatment group was included
Tapia 2012	Randomised controlled trial of prophylactic CPAP compared with standard care (oxygen by head-box or nasal cannula when indication). CPAP was followed by surfactant via INSURE technique (intubate-surfactant-extubate), and standard care was followed by mechanical ventilation and surfactant
Tooley 2003	Study included infants of 25 to 28 weeks' gestation who were intubated at birth, given a single dose of surfactant and positive pressure ventilation, then randomly assigned at about 1 hour of age to extubation, to nasal CPAP or to continued conventional IPPV. No criteria for the diagnosis of RDS were given

DATA AND ANALYSES

Comparison 1. CDP vs standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure (by death and use of additional ventilatory assistance, by blood gas criteria or by transfer to a neonatal intensive care unit)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Death or use of additional ventilatory support	6	355	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.52, 0.81]
1.2 Death or respiratory failure by blood gas criteria	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.32, 0.90]
1.3 Death or transfer to a neonatal intensive care unit	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.30, 0.78]
2 Use of additional ventilatory assistance	5	314	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.56, 0.91]
3 Transfer to a neonatal intensive care unit	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.30, 0.75]
4 Mortality	6	355	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.32, 0.87]
5 Mortality ≤ 1500 g	2	32	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.38, 1.20]
6 Mortality > 1500 g	2	60	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.07, 0.84]
7 Duration of supplemental oxygen (days)	2	76	Mean Difference (IV, Fixed, 95% CI)	0.65 [-1.86, 3.15]
8 Any pneumothorax	6	355	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [1.39, 5.04]
9 Pneumothorax occurring after allocation	6	351	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [1.26, 4.65]
10 Use of surfactant	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.12, 1.48]
11 Bronchopulmonary dysplasia at 28 days in survivors	3	260	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.44, 3.39]
12 Death or severe disability	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Death or severe disability	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.34, 5.17]
12.2 Death or severe disability < 1500 g	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Death or disability ≥ 1500 g	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.31, 4.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.4 Death or severe disability < 32 weeks	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.5 Death or severe disability ≥ 32 weeks	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.42, 5.64]
13 Severe disability	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.24, 4.57]
14 Any disability	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.31, 1.21]
15 Cerebral palsy	1	36	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 97.37]

Analysis 1.1. Comparison 1 CDP vs standard care, Outcome 1 Treatment failure (by death and use of additional ventilatory assistance, by blood gas criteria or by transfer to a neonatal intensive care unit).

Analysis 1.2. Comparison 1 CDP vs standard care, Outcome 2 Use of additional ventilatory assistance.

Analysis 1.3. Comparison 1 CDP vs standard care, Outcome 3 Transfer to a neonatal intensive care unit.

Analysis 1.4. Comparison 1 CDP vs standard care, Outcome 4 Mortality.

Analysis 1.5. Comparison 1 CDP vs standard care, Outcome 5 Mortality ≤ 1500 g.

Analysis 1.6. Comparison 1 CDP vs standard care, Outcome 6 Mortality > 1500 g.

Analysis 1.7. Comparison 1 CDP vs standard care, Outcome 7 Duration of supplemental oxygen (days).

Analysis 1.8. Comparison 1 CDP vs standard care, Outcome 8 Any pneumothorax.

Analysis 1.9. Comparison 1 CDP vs standard care, Outcome 9 Pneumothorax occurring after allocation.

Analysis 1.10. Comparison 1 CDP vs standard care, Outcome 10 Use of surfactant.

Analysis 1.11. Comparison 1 CDP vs standard care, Outcome 11 Bronchopulmonary dysplasia at 28 days in survivors.

Analysis 1.12. Comparison 1 CDP vs standard care, Outcome 12 Death or severe disability.

Analysis 1.13. Comparison 1 CDP vs standard care, Outcome 13 Severe disability.

Analysis 1.14. Comparison 1 CDP vs standard care, Outcome 14 Any disability.

Analysis 1.15. Comparison 1 CDP vs standard care, Outcome 15 Cerebral palsy.

Comparison 2. CNP vs standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure (death or use of additional ventilatory assistance)	2	81	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.41, 0.90]
2 Use of additional ventilatory assistance	2	81	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.46, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Mortality	2	81	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.31, 2.09]
4 Pneumothorax after allocation	2	81	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.63, 8.12]
5 Bronchopulmonary dysplasia at 28 days in survivors	1	52	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.42]
6 Death or severe disability	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.34, 5.17]
7 Severe disability	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.23, 4.31]
8 Any disability	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.31, 1.21]
9 Cerebral palsy	1	36	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 97.37]

Analysis 2.1. Comparison 2 CNP vs standard care, Outcome 1 Failure (death or use of additional ventilatory assistance).

Analysis 2.2. Comparison 2 CNP vs standard care, Outcome 2 Use of additional ventilatory assistance.

Analysis 2.3. Comparison 2 CNP vs standard care, Outcome 3 Mortality.

Analysis 2.4. Comparison 2 CNP vs standard care, Outcome 4 Pneumothorax after allocation.

Analysis 2.5. Comparison 2 CNP vs standard care, Outcome 5 Bronchopulmonary dysplasia at 28 days in survivors.

Analysis 2.6. Comparison 2 CNP vs standard care, Outcome 6 Death or severe disability.

Analysis 2.7. Comparison 2 CNP vs standard care, Outcome 7 Severe disability.

Analysis 2.8. Comparison 2 CNP vs standard care, Outcome 8 Any disability.

Analysis 2.9. Comparison 2 CNP vs standard care, Outcome 9 Cerebral palsy.

Comparison 3. CPAP vs standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure (by death or use of additional ventilatory assistance)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Death or use of additional ventilation	3	250	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.45, 0.81]
1.2 Death or failure by blood gas criteria	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.32, 0.90]
1.3 Death or transfer to a neonatal intensive care unit	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.30, 0.78]
2 Use of additional ventilatory assistance	2	209	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.47, 0.89]
3 Mortality	2	199	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.23, 1.16]
4 Mortality $\leq$ 1500 g	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.52, 1.92]
5 Mortality $>$ 1500 g	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.59]
6 Any pneumothorax	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [0.29, 22.88]
7 Pneumothorax occurring after allocation	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.06, 12.89]

Analysis 3.1. Comparison 3 CPAP vs standard care, Outcome 1 Treatment failure (by death or use of additional ventilatory assistance).

Analysis 3.2. Comparison 3 CPAP vs standard care, Outcome 2 Use of additional ventilatory assistance.

Analysis 3.3. Comparison 3 CPAP vs standard care, Outcome 3 Mortality.

Analysis 3.4. Comparison 3 CPAP vs standard care, Outcome 4 Mortality ≤ 1500 g.

Analysis 3.5. Comparison 3 CPAP vs standard care, Outcome 5 Mortality > 1500 g.

Analysis 3.6. Comparison 3 CPAP vs standard care, Outcome 6 Any pneumothorax.

Analysis 3.7. Comparison 3 CPAP vs standard care, Outcome 7 Pneumothorax occurring after allocation.

Comparison 4. Early application of CDP vs standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure (death or use of additional ventilatory assistance)	3	121	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.44, 0.79]
2 Mortality	2	70	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.05]

Analysis 4.1. Comparison 4 Early application of CDP vs standard care, Outcome 1 Failure (death or use of additional ventilatory assistance).

Analysis 4.2. Comparison 4 Early application of CDP vs standard care, Outcome 2 Mortality.

Comparison 5. CDP vs standard care - excluding Rhodes (quasi-random)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure (death or use of additional ventilatory assistance)	5	314	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.54, 0.86]
2 Mortality	4	263	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.26, 1.56]

Analysis 5.1. Comparison 5 CDP vs standard care - excluding Rhodes (quasi-random), Outcome 1 Failure (death or use of additional ventilatory assistance).

Analysis 5.2. Comparison 5 CDP vs standard care - excluding Rhodes (quasi-random), Outcome 2 Mortality.

Comparison 6. CDP vs standard care - excluding Belenky (low quality)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure (death or use of additional ventilatory assistance)	5	304	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.47, 0.80]
2 Mortality	5	304	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.34, 1.11]

Analysis 6.1. Comparison 6 CDP vs standard care - excluding Belenky (low quality), Outcome 1 Failure (death or use of additional ventilatory assistance).

Analysis 6.2. Comparison 6 CDP vs standard care - excluding Belenky (low quality), Outcome 2 Mortality.

APPENDICES

Appendix 1. Cochrane Neonatal standard search strategy

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

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

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

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

WHAT'S NEW

Date	Event	Description
30 April 2015	New search has been performed	This updates the review "Continuous distending pressure for respiratory distress in preterm infants", published in <i>The Cochrane Library</i> (Ho 2002). Definitions for little, moderate and substantial heterogeneity were modified according to the recommendations provided in the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> (Deeks 2011)
30 April 2015	New citation required but conclusions have not changed	Four new studies excluded. No change to conclusions

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 3, 2000

Date	Event	Description
12 November 2009	New citation required but conclusions have not changed	Follow-up data at 9 to 15 years included for 1 trial Prespecified outcome, neurodevelopmental outcome in childhood, was defined
12 November 2009	New search has been performed	This updates the review "Continuous distending pressure for respiratory distress syndrome in preterm infants", published in the Cochrane Database of Systematic Reviews, 2004, Issue 1 Literature search repeated in October 2009 No new studies found
24 May 2008	New search has been performed	This updates the review "Continuous distending pressure for respiratory distress syndrome in preterm infants", published in the Cochrane Database of Systematic Reviews, 2004, Issue 1 (Ho 2002). The title has been modified slightly to read "Continuous distending pressure for respiratory distress in preterm infants" Primary outcome modified and additional outcomes included. Search was repeated, and 1 new trial has been included No change to the conclusions
10 April 2008	Amended	Converted to new review format
27 August 2004	New search has been performed	This review updates review "Continuous distending pressure for respiratory distress syndrome in preterm infants", last updated in <i>The Cochrane Library</i> , 2002, Issue 2 (Ho 2002) Literature search repeated; no further trials eligible for inclusion were found. No changes to the overall conclusions
7 February 2002	New citation required and conclusions have changed	Substantive amendments

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DECLARATIONS OF INTEREST

None.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Premature; Infant, Low Birth Weight; Intermittent Positive-Pressure Ventilation [adverse effects]; Outcome Assessment, Health Care; Pneumothorax [etiology]; Positive-Pressure Respiration [*methods]; Pulmonary Surfactants [therapeutic use]; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn [mortality] [*therapy]; Selection Bias

MeSH check words

Humans; Infant, Newborn