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Meyer MP, Nevill E, Wong MM

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(Review)

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[Intervention Review]

Provision of respiratory support compared to no respiratory support before cord clamping for preterm infants

Michael P Meyer¹, Elizabeth Nevill², Maisie M Wong²¹Department of Pediatrics, Middlemore Hospital/CMDHB, Auckland, New Zealand. ²Neonatal Pediatrics, Middlemore Hospital, Auckland, New Zealand**Contact:** Michael P Meyer, Department of Pediatrics, Middlemore Hospital/CMDHB, Auckland, New Zealand.
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ABSTRACT

Background

Placental transfusion (by means of delayed cord clamping (DCC), cord milking, or cord stripping) confers benefits for preterm infants. It is not known if providing respiratory support to preterm infants before cord clamping improves outcomes.

Objectives

To assess the efficacy and safety of respiratory support provided during DCC compared with no respiratory support during placental transfusion (in the form of DCC, milking, or stripping) in preterm infants immediately after delivery.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL, 2017, Issue 5), MEDLINE via PubMed (1966 to 19 June 2017), Embase (1980 to 19 June 2017), and CINAHL (1982 to 19 June 2017). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials.

Selection criteria

Randomized, cluster randomized, or quasi-randomized controlled trials enrolling preterm infants undergoing DCC, where one of the groups received respiratory support before cord clamping and the control group received no respiratory support before cord clamping.

Data collection and analysis

All review authors assisted with data collection, assessment, and extraction. Two review authors assessed the quality of evidence using the GRADE approach. We contacted study authors to request missing information.

Main results

One study fulfilled the review criteria. In this study, 150 preterm infants of less than 32 weeks' gestation undergoing 60 second DCC were randomized to a group who received respiratory support in the form of continuous positive airway pressure (CPAP) or positive pressure ventilation during DCC and a group that did not receive respiratory support during the procedure. Mortality during hospital admission was not significantly different between groups with wide confidence intervals (CI) for magnitude of effect (risk ratio (RR) 1.67, 95% CI 0.41 to 6.73). The study did not report neurodevelopmental disability and death or disability at two to three years of age. There were no significant differences between groups in condition at birth (Apgar scores or intubation in the delivery room), use of inotropic agents (RR 1.25, CI 0.63 to 2.49), and receipt of blood transfusion (RR 1.03, 95% CI 0.70 to 1.54). In addition, there were no significant differences in the incidences

of any intraventricular haemorrhage (RR 1.50, 95% CI 0.65 to 3.46) and severe intraventricular haemorrhage (RR 1.33, 95% CI 0.31 to 5.75). Several continuous variables were reported in subgroups depending on method of delivery. Unpublished data for each group as a whole was made available and showed peak haematocrit in the first 24 hours and duration of phototherapy did not differ significantly. Overall, the quality of evidence for several key neonatal outcomes (e.g. mortality and intraventricular haemorrhage) was low because of lack of precision with wide CIs.

Authors' conclusions

The results from one study with wide CIs for magnitude of effect do not provide evidence either for or against the use of respiratory support before clamping the umbilical cord. A greater body of evidence is required as many of the outcomes of interest to the review occurred infrequently. Similarly, the one included study cannot answer the question of whether the intervention is or is not harmful.

PLAIN LANGUAGE SUMMARY

Providing breathing support before clamping the umbilical cord in preterm babies

Review question: do preterm babies benefit from receiving breathing support before the cord is clamped?

Background: allowing preterm infants to receive blood from the placenta after birth and before clamping the umbilical cord has health benefits for the baby and is not harmful for the mother. Most babies will start breathing or crying (or both) before the cord is clamped. However, some babies do not establish regular breathing during this time. After clamping the cord, most preterm babies are given some form of breathing support like continuous positive airway pressure (CPAP). CPAP applies continuous low air pressure to keep the airways open in babies who can breathe on their own. The question for this review was whether it was beneficial to start the breathing support before the cord is clamped.

Study characteristics: we searched medical databases and found one study for inclusion in this review. Preterm infants born before 32 weeks' gestation (32 weeks from the first day of the woman's last period (menstruation) to the current date) who had clamping of the umbilical cord delayed for 60 seconds after birth were selected at random to enter a group of babies who received breathing support and a group of babies who did not receive breathing support. The breathing support was given after birth of the baby and before the cord was clamped. Breathing support was the use of CPAP for infants breathing on their own or applying intermittent airway **pressure** to expand the lungs in babies not breathing well on their own. Most of the study infants (83%) were delivered by caesarean section.

Key results: the single study included in the review did not provide sufficient evidence either for or against the use of breathing support before cord clamping.

Quality of evidence: the quality of evidence was low, mainly because more infants need to be studied for definite conclusions.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Respiratory support compared with no respiratory support before cord clamping in preterm infants

Respiratory support compared with no respiratory support before cord clamping in preterm infants

Patient or population: preterm infants

Settings: undergoing delayed cord clamping

Intervention: respiratory support

Comparison: no respiratory support

Outcomes	Relative effect (95% CI)	No of participants	Quality of the evidence (GRADE)	Comments
Mortality ≤ 2 years after hospital discharge	RR 1.67 (0.41 to 6.73)	150	⊕⊕⊕⊖ Low ¹	Secondary study outcome.
Inotropic support for hypotension	RR 1.25 (0.63 to 2.49)	150	⊕⊕⊕⊖ Low ¹	-
Peak haematocrit	MD 0.20 (-1.85 to 2.25)	150	⊕⊕⊕⊖ Moderate ³	Primary outcome.
Blood transfusion during neonatal admission	RR 1.03 (0.70 to 1.54)	150	⊕⊕⊕⊖ Moderate	40% with this outcome
Phototherapy for hyperbilirubinaemia	MD 0.20 (-0.31 to 0.71)	150	⊕⊕⊕⊖ Moderate ³	From unpublished data
Intraventricular haemorrhage (of any grade)	RR 1.50 (0.65 to 3.46)	150	⊕⊕⊕⊖ Low ¹	Secondary outcome.
Severe intraventricular haemorrhage grade 3 or 4	RR 1.33 (0.31 to 5.75)	150	⊕⊕⊕⊖ Very low ²	Uncommon secondary outcome.

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

In the published report, results were presented according to method of delivery. For categorical variables (e.g. mortality), the RR was calculated for the delayed cord clamping with ventilation support (intervention) and delayed cord clamping (control) groups as a whole. For continuous variables (e.g. haematocrit), the authors provided unpublished data that enabled whole group statistics to be determined.

¹Downgraded one level due to lack of precision with wide confidence intervals.

²Downgraded two levels due to lack of precision (confidence intervals included both important benefit and harm). The optimal information size for a 30% risk reduction with 80% power and 95% confidence intervals was 3280 infants per group.

³Unpublished data.

BACKGROUND

Facilitating placental transfusion before cord clamping has potential benefits for term infants (McDonald 2013), and is increasingly recommended for preterm infants (Perlman 2010; Rabe 2012; McAdams 2014). Reported benefits for preterm infants include reduction in the number of blood transfusions; decreased incidence of intraventricular haemorrhage (IVH) (of all grades); reduced requirement for inotrope support; and improved important neonatal outcomes such as necrotizing enterocolitis and late-onset sepsis (Rabe 2000; Mercer 2006; Hosono 2008; Kakkilaya 2008; Oh 2011; Rabe 2012).

Different methods are employed to facilitate placental transfusion, including delayed cord clamping (DCC), cord milking, and cord stripping after the cord has been clamped (Hosono 2008; Rabe 2012; March 2013). To date, few direct comparisons between DCC and cord milking have taken place (Rabe 2012; Katheria 2015). Although milking and stripping can be carried out quickly, recommendations for the timing of DCC vary from 30 seconds to one minute or longer for preterm infants (Raju 2013; ACOG 2012). It may be relevant to define early or late clamping according to whether or not respiration is established (Redmond 1965). A limited number of studies has indicated that less blood is retained in the placenta and haematocrit is increased in infants undergoing DCC when breathing is established (Redmond 1965; Kjeldsen 1967; Philip 1973). One study reported placental transfusion in relation to the onset of respiration in small numbers of preterm and low birth weight infants (Kjeldsen 1967). Less blood was retained within the placenta (and by inference, greater placental transfusion occurred) when respiration was established before cord clamping, and placental transfusion appeared to increase over time after birth. This latter finding was thought to reflect that preterm infants took longer to establish regular breathing than term infants.

Description of the condition

Preterm infants show variable respiratory effort while DCC is occurring (Kjeldsen 1967; Nevill 2015). Animal work indicates that positive pressure ventilation is beneficial for anaesthetized preterm lambs before DCC and helps reduce fluctuations in cerebral blood flow (Bhatt 2013). Likewise, observational studies in term and preterm infants confirm better outcomes in infants who establish spontaneous respiration before clamping (Ersdal 2014; Nevill 2015). Preterm infants who were not breathing during DCC had an increased incidence of chronic lung disease and IVH. It is unclear whether preterm infants who were not breathing had more severe respiratory distress or were compromised by lack of placental transfusion. It is also unclear to what extent providing artificial breaths will allow lung expansion to occur before clamping. During DCC, it is thought that placental perfusion remains intact to provide for the metabolic needs of the infant. At the same time, the placenta provides a reservoir of blood to fill the pulmonary vascular bed as the lungs are inflated. As this happens, a rapid drop in pulmonary vascular resistance occurs (Dawes 1953). Venous return from the lungs enters the left atrium and maintains left atrial filling, providing preload (i.e. increased end-diastolic volume) for left ventricular output and subsequent cerebral perfusion. Ductal shunting rapidly reverses from the in utero pattern of right to left to the dominant postnatal pattern of left to right (Bhatt 2013). This allows some of the left ventricular output to enter the low-resistance pulmonary circulation, thus providing a low-resistance pathway and reduced left ventricular afterload

(i.e. a lower end load against which the left ventricle contracts) during this transitional phase. In addition, the right ventricle pumps into the pulmonary circulation when pulmonary vascular resistance has dropped with lung expansion. Thus, both right and left ventricular afterloads are reduced (Hooper 2015). The net effect of all of this includes increased blood volume and more stable perfusion, especially to the brain (Aladangady 2006; Baenziger 2007; Meyer 2012; Sommers 2012; Bhatt 2013). This is important, as the preterm brain has limited autoregulation. Periods of decreased cerebral perfusion may be followed by reperfusion, and this can result in germinal matrix haemorrhage (Kluckow 2000; Soul 2007; Noori 2014). Facilitating physiological changes during the transition could explain improved outcomes with DCC. In contrast, if respiration is not established and the lungs are not inflated, it follows that DCC may provide less benefit, although evidence shows that placental transfusion still occurs (Redmond 1965; Philip 1977). This raises the question of whether providing respiratory support before clamping could be beneficial and could support physiological changes. Conceivably, breathing assistance could be given to all preterm infants undergoing DCC or only to those who fail to establish respiration. The simplest methods of support would include positive pressure ventilation and continuous positive airway pressure (CPAP) via face mask or nasal prong. More invasive strategies, such as use of a laryngeal mask or endotracheal intubation and even surfactant, are conceivable but would require major deviations from current practice. For this review, our aim was to determine whether providing some form of respiratory support during DCC is beneficial for preterm infants.

Description of the intervention

The intervention was respiratory support provided for preterm infants while DCC was taking place. Types of respiratory assistance were CPAP via face mask or nasal prong and positive pressure ventilation via face mask, as well as more invasive strategies such as endotracheal intubation and use of a laryngeal mask. Tactile stimulation was not considered as respiratory support.

To provide a suitable firm surface for respiratory support, various techniques have been described (Winter 2017; Duley 2018). In some instances, a trolley is placed alongside the mother. This may be a purpose built trolley with resuscitation equipment attached (Katheria 2016), or a trolley with the required equipment (e.g. oxygen blender and T-piece resuscitator) attached to a pole or pendant (Winter 2017; ABC study (ACTRN12615001026516); te Pas 2016 (NTR6095); VentFirst (NCT02742454)). At caesarean section, a heated gel mattress placed on the maternal thighs has also been found suitable (Katheria 2016). A resuscitaire alongside the mother's bed for vaginal births has also been described (Duley 2018). Temperature maintenance is aided using a plastic wrap, heated gel mattress, or radiant warmer.

Techniques for facilitating placental transfusion have been described in detail elsewhere (Rabe 2012; Al-Wassia 2015). Cord milking or stripping studies have described variability in terms of speed of milking, the number of times the milking was performed, the length of cord milked, and whether the cord was milked before or after it was clamped (Rabe 2012; Al-Wassia 2015). Cord stripping was regarded as milking after the cord was clamped.

How the intervention might work

Facilitating respiration during DCC could increase placental transfusion and stabilize the transitional circulation by providing increased preload to both ventricles and reducing afterload. This in turn may result in less fluctuation in cerebral blood flow and decreased likelihood of IVH.

Why it is important to do this review

There are important health benefits for infants undergoing DCC. Although it appears that most infants breathe during the procedure, infants who do not may be subject to worse outcomes. Facilitating a stable transition by providing breathing support or resuscitation could result in reduced IVH, and improved neurodevelopmental and other neonatal outcomes. As noted in the review by Rabe (Rabe 2012), one rationale for early clamping is that it allows respiratory support to commence, but few data are available on respiratory outcomes and the onset of respiration, particularly in preterm infants (Kjeldsen 1967). This highlights the need for additional studies in this area.

OBJECTIVES

To assess the efficacy and safety of respiratory support provided during delayed cord clamping (DCC) compared with no respiratory support during placental transfusion (in the form of DCC, milking, or stripping) in preterm infants immediately after delivery.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCT), cluster-randomized, and quasi-randomized studies and applied no language or publication status restrictions. The review included only studies in which DCC or placental transfusion was a planned intervention for all participants (i.e. did not include studies in which the control group did not receive intervention to facilitate placental transfusion).

Types of participants

Preterm infants (less than 37 weeks' gestation) undergoing placental transfusion (i.e. DCC, cord milking, or cord stripping) when the treatment group received placental transfusion (i.e. DCC) with ventilation support (V-DCC) and the control group received placental transfusion (i.e. DCC, cord milking, or cord stripping) without ventilation support (DCC).

Types of interventions

Breathing support included CPAP via face mask, nasal prongs, or nasopharyngeal tube, and positive pressure ventilation provided by face mask, endotracheal tube, or laryngeal mask. Respiratory support was to be provided before cord clamping. Potential comparison groups included infants receiving DCC without support, and infants undergoing cord milking or stripping without support. The intervention could be applied to all preterm infants or only to infants deemed to be not breathing or in need of resuscitation. The intervention above was to be reflected in subgroup analyses, which included types of support provided,

whether support was applied to all infants, or only infants not breathing.

Types of outcome measures

Primary outcomes

- Mortality up to two years after hospital discharge - to be reported as death before 28 days, death before hospital discharge, or death after discharge.
- Neurodevelopmental disability (mild, moderate, or severe) at age 18 to 24 months (Doyle 2010).
- Death or neurodevelopmental disability at two to three years of age (Doyle 2010).

Secondary outcomes

- Condition at birth.
 - Apgar score at one, five, and 10 minutes.
 - Cord gas base deficit greater than 10 mmol/L.
 - Need for intubation in delivery room or within first hour of life.
 - Cardiac compression in delivery room.
- Cardiovascular measures and measures of transitional circulation.
 - Volume administration in the form of blood products or crystalloid for hypotension (as defined by research authors) during first 24 hours of life, recorded as number of boluses and as total volume administered.
 - Inotropic support for hypotension (mean arterial pressure below gestation in weeks or as defined by research authors) during first 24 hours of life.
 - Superior vena cava (SVC) blood flow (mL/kg/minute) in the first 24 hours of life (Kluckow 2000).
 - Cerebral near-infrared spectroscopy (NIRS) (total oxygenation index, fractional total oxygen extraction (FTOE) during first 24 hours of life) (van Bel 2008).
 - Urine output (mL/kg/hour) during first 48 hours of life.
 - Metabolic acidosis (base deficit greater than 10 mmol/L) during first 48 hours of life.
 - Poor systemic blood flow during first 24 hours. This included any of the following: volume administration, therapy for low blood pressure, low SVC flow (Groves 2008), abnormal NIRS (van Bel 2008), or decreased urine output (less than 1 mL/kg/hour).
- Haematological outcomes.
 - Haemoglobin (g/L) or haematocrit at birth and within 24 hours of birth.
 - Blood transfusion during neonatal admission (number of transfusions and volume transfused).
 - Treatment (phototherapy or other) for hyperbilirubinaemia.
- Respiratory outcomes.
 - Use of surfactant in the first 48 hours of life.
 - Days of oxygen therapy.
 - CPAP days.
 - Ventilation days.
 - Oxygen requirement at 28 days.

- Bronchopulmonary dysplasia as defined by respiratory support or oxygen requirement at 36 weeks' corrected gestational age.
- Bronchopulmonary dysplasia at 36 weeks' postmenstrual age according to a physiological definition (Walsh 2004).
- Other neonatal outcomes.
 - IVH (of any grade) (Papile 1978).
 - Severe IVH grade 3 or 4 (Papile 1978).
 - Periventricular leukomalacia.
 - Necrotizing enterocolitis Bell's stage 2 or greater (Bell 1978).
 - Retinopathy all stages and stage 3 and greater.
 - Sepsis (early- and late-onset more than 48 hours): isolation of an organism from at least one blood or cerebrospinal fluid (CSF) culture with the decision to treat with antibiotics with therapeutic intent against this organism.
 - Pharmacological treatment or surgical ligation for patent ductus arteriosus.
 - Length of hospital stay (days).

Search methods for identification of studies

Electronic searches

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

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 5) in the Cochrane Library; MEDLINE via PubMed (1966 to 19 June 2017); Embase (1980 to 19 June 2017); and CINAHL (1982 to 19 June 2017) using the following search terms: ((umbilicus OR umbilical OR cord OR navel-string) AND (clamp OR cut OR ligation OR ligature OR delay* OR defer* OR time OR intact OR late OR early OR immediate) AND (support OR breathing OR respiration OR resuscitation OR continuous positive airway pressure OR CPAP OR positive pressure ventilation OR ventilate*)), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for the full search strategies for each database). We applied no language restrictions.

Searching other resources

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

Data collection and analysis

Selection of studies

All three review authors working independently reviewed search results and each search result was independently reviewed by at least two of the authors. We examined title and abstract in the first instance, then full text if appropriate. We kept a record of the number of studies screened at each step. Disagreements were resolved by consensus and, if necessary, through contact with study authors. Should this fail, the third review author was to make the decision. If a final arbiter was needed, we planned to refer the matter to the Cochrane Neonatal Review Group.

We collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We

recorded the selection process in sufficient detail to complete a PRISMA flow diagram.

Data extraction and management

Two review authors working independently extracted data from included studies. One review author (MM) extracted the data, and the other (MW) checked the entries. We collected participant demographics (including gestation) and types of interventions (such as mode of respiratory support). We detailed comparison groups (such as DCC without support) and outcomes (in line with the proposed [Primary outcomes](#); and [Secondary outcomes](#)) and noted study design. Any disagreements about data extraction were to be resolved by reaching consensus, seeking additional details from study authors, deferring to the opinion of the third review author, and referring the matter to the Neonatal Review Group, in that order. In addition, we contacted the study author to request further data. We used study information to create a [Characteristics of included studies](#) table.

Assessment of risk of bias in included studies

Two review authors (MM and MW) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- 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 a third review author. See [Appendix 2](#) for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We used risk ratios (RR) and 95% confidence intervals (CI) for categorical data, and mean differences (MD) between groups for continuous data where provided. We aimed to calculate the number needed to treat for an additional beneficial or harmful outcome.

Unit of analysis issues

The nature of the intervention precluded randomization of infants to more than one group. We planned to include cluster-randomized studies in this review. We aimed to provide repeat measures (e.g. for haematocrit or repeat SVC blood flow); however, we planned to restrict our review to results of these measures to 48 hours after birth (as noted in the [Secondary outcomes](#)).

Dealing with missing data

We planned to ignore data that appeared to be missing. For data deemed not missing at random, we aimed to assign a poor outcome if dichotomous, or the mean value imputed if continuous. We sought to detail any assumptions made and any sensitivity analyses carried out with and without missing data.

Assessment of heterogeneity

We aimed to report heterogeneity in the following groups: less than 25%: none; 25% to 49%: low; 50% to 74%: moderate; and 75% and above: high.

Assessment of reporting biases

We searched for unpublished studies in trial registries. We aimed to prepare funnel plots (if we found at least 10 trials) and to perform Egger's test.

Data synthesis

We aimed to undertake meta-analysis if studies were sufficiently similar in terms of participants, interventions, and outcome measures. If at least two studies were included in the meta-analysis, we planned to calculate typical RRs and risk differences, as well as number needed to treat for an additional beneficial effect or an additional harmful effect. For continuous data, we sought to calculate MDs if studies used the same scales or standardized mean differences if studies used difference scales and include 95% CIs. We planned to undertake analysis of studies with high risk of bias omitted to see if review results were affected. We used fixed-effect models and aimed to note the degree of heterogeneity (see [Assessment of heterogeneity](#)). When heterogeneity was high, we planned to undertake sensitivity analysis to identify sources of bias.

Quality of evidence

We used the GRADE approach, as outlined in the [GRADE Handbook \(Schünemann 2013\)](#), to assess the quality of evidence for the following (clinically relevant) outcomes.

- Mortality (in hospital).
- IVH (any grade).
- Severe IVH grade 3 or 4.
- Use of inotropic agents.
- Blood transfusion.
- Haematocrit.
- Days of phototherapy.

Two review authors independently assessed the quality of the evidence for each outcome. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the [GRADEpro GDT](#) Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence into one of four grades:

- 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.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.

- Type of respiratory support provided to infants undergoing DCC: CPAP (via face mask or nasal prongs or nasopharyngeal tube) and positive pressure ventilation (by face mask or laryngeal mask or endotracheal tube).
- Gestational age: gestational age less than 28 weeks and gestational age 28 weeks or greater.
- Infants undergoing DCC that were breathing versus infants undergoing DCC that were not breathing.

Sensitivity analysis

We planned to perform a meta-analysis of relevant studies to examine the effect of including only certain available studies that met most or all eligibility criteria and omitting those studies that did not. We aimed to undertake a sensitivity analysis to examine risk of bias.

RESULTS

Description of studies

Results of the search

We identified 1809 records through database searching and 39 additional records through other sources. After removing duplicates, 1560 records remained. We excluded 1552 records as obviously irrelevant on reading the titles or abstracts (or both), leaving 8 potentially eligible studies. After reading the full text, we excluded four studies, with reasons ([Characteristics of excluded studies](#) table), and identified 3 ongoing studies ([Characteristics of ongoing studies](#)). We included one study ([Characteristics of included studies](#)) (see [Figure 1](#)).

Figure 1. Study flow diagram.

Included studies

One study met the inclusion criteria (see [Characteristics of included studies](#) table) ([Katheria 2016](#)). This single-centre RCT performed in San Diego, USA, studied preterm infants of less than 32 weeks'

gestation delivered after caesarean or vaginal birth. All infants underwent 60 seconds of DCC while placed on a trolley that was at the level of the incision for caesarean delivery or below the level of the placenta after vaginal birth. Infants were randomized

to a standard group (DCC group) or an intervention group (V-DCC). Infants in the V-DCC group received ventilation support in the form of face mask CPAP, or if not displaying regular chest movement, positive pressure ventilation via face mask with room air. Infants in the V-DCC group had a carbon dioxide detection monitor attached to the circuit to assess the effectiveness of respiration better. Infants in the DCC group were dried and given gentle stimulation to help establish respiration. There were 75 infants in each group; 83% of study infants were delivered by caesarean section. The primary outcome was maximum haematocrit in the first 24 hours and neonatal outcomes including IVH, in-hospital mortality, blood transfusion, and jaundice were reported. In addition, a variety of physiological measures of the transitional circulation were undertaken.

Excluded studies

We excluded four studies (see [Characteristics of excluded studies](#) table). The control group in the study of [Aladangady 2006](#) was randomized to early cord clamping, as were the controls in the Cord pilot trial ([Duley 2018](#)). One of the studies was observational ([Phillippos 2017](#)), and the other was a pilot feasibility study without a randomized control group ([Winter 2017](#)).

Ongoing studies

There were three ongoing studies, the ABC study ([ABC study \(ACTRN12615001026516\)](#)), the VentFirst study ([VentFirst \(NCT02742454\)](#)), and a feasibility study using the Con-Cord table ([te Pas 2016 \(NTR6095\)](#)) (see [Characteristics of ongoing studies](#) table).

Risk of bias in included studies

Overall risk of bias was low.

Allocation

Randomization sequence was computer generated. Allocation of intervention was concealed using numbered sealed envelopes (low risk of bias).

Blinding

Researchers making assessments and measurements were blinded to group allocation at infants' births, but clinicians involved during

transition in the delivery room were not blinded to group allocation and may have been the same clinicians caring for the infants (high risk of bias).

Incomplete outcome data

All infants were accounted for (low risk of bias).

Selective reporting

There was no evidence of selective reporting (low risk of bias). Study outcomes were those reported in the protocol (NCT02231411; [Katheria 2016](#)).

Other potential sources of bias

There were no other potential sources of bias apparent.

Effects of interventions

See: [Summary of findings for the main comparison Respiratory support compared with no respiratory support before cord clamping in preterm infants](#)

One RCT met the inclusion criteria. Reported outcomes were mainly short-term neonatal outcomes, including in-hospital mortality, but not neurodevelopmental outcomes. Study results were reported according to the mode of delivery and most of the infants undergoing DCC were caesarean births. For categorical data, results for each group (i.e. V-DCC or DCC) could be calculated from the published study. However, this could not be done for continuous data. Subsequently, the authors provided unpublished information, which enabled analysis of continuous data for the V-DCC and DCC groups as a whole.

See [Summary of findings for the main comparison](#).

Primary outcomes

Mortality

There was no significant difference in mortality before hospital discharge between groups (5/75 in the V-DCC group versus 3/75 in the DCC group; RR 1.67, 95% CI 0.41 to 6.73; [Analysis 1.1](#); [Figure 2](#)). The study did not report death before 28 days or death after discharge.

Figure 2. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.1 Mortality during neonatal admission.

Neurodevelopmental disability

The study did not report neurodevelopmental disability.

Death or neurodevelopmental disability at two to three years of age

The study did not report death or neurodevelopmental disability at two to three years of age.

Secondary outcomes

Condition at birth

Apgar score at one, five, and 10 minutes

There were no significant differences in Apgar score between the V-DCC and DC groups (unpublished data) and medians were 8 at five minutes in both groups.

The study did not report Apgar score at 10 minutes.

Cord blood base deficit greater than 10 mmol/L

Cord blood base deficit greater than 10 mmol/L was not reported.

Need for intubation in delivery room or within first hour of life

Intubation rates in the delivery room were not significantly different (27/75 in the V-DCC group versus 33/75 in the DCC group; RR 0.82, 95% CI 0.55 to 1.21; [Analysis 1.2](#); [Figure 3](#)).

Figure 3. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.2 Need for intubation in delivery room.

Cardiac compression in delivery room

No cases received cardiac compressions during resuscitation at birth (unpublished information).

Cardiovascular measures and measures of transitional circulation

Volume administration in the form of blood products or crystalloid for hypotension

Receipt of fluid bolus for volume administration was not significantly different between groups (20 cases in the V-DCC group versus 21 in the DCC group; unpublished data).

Inotropic support for hypotension

Use of inotropic agents in the two groups was not significantly different (15/75 in the V-DCC group and 12/75 in the DCC group; RR 1.25, 95% CI 0.63 to 2.49; [Analysis 1.3](#); [Figure 4](#)).

Figure 4. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.3 Inotropic support for hypotension.

Superior vena cava blood flow

There was no significant difference between groups in SVC blood flow (reported as subgroups according to delivery method).

Cerebral near-infrared spectroscopy

There was no significant difference between groups in cerebral NIRS readings (reported graphically).

Urine output

There was no significant difference between groups in urine output (reported as subgroups according to delivery method).

Metabolic acidosis

There was no significant difference in umbilical venous pH when the groups as a whole were analyzed (MD 0.02, 95% CI -0.05 to 0.01; unpublished data).

Poor systemic blood flow during first 24 hours

The study did not report poor systemic flow.

Haematological outcomes

Haemoglobin or haematocrit at birth and within 24 hours of birth

The study found no significant difference in peak haematocrit within 24 hours of birth (according to method of delivery) between groups. When analyzed for the V-DCC group versus DCC group as a whole, the MD was 0.20 (95% CI -1.85 to 2.25; unpublished data; [Analysis 1.4](#); [Figure 5](#)).

Figure 5. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.4 Peak haematocrit in first 24 hours [%].

Blood transfusion during neonatal admission

In the V-DCC group, 30 infants were transfused compared to 29 in the DCC group (RR 1.03, 95% CI 0.70 to 1.54; [Analysis 1.5](#); [Figure 6](#)).

The volume transfused was not specified. There was no significant difference in number of transfusions (MD 1.31, 95% CI -2.50 to 5.12; unpublished).

Figure 6. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.5 Blood transfusion during neonatal admission.

Treatment (phototherapy or other) for hyperbilirubinaemia

There was no significant difference in duration of phototherapy for hyperbilirubinaemia. Among caesarean deliveries, the mean duration was 4.1 days in the V-DCC group and 3.8 days in the DCC

group ($P = 0.32$). When the unpublished data were reviewed, the MD was 0.20 (95% CI -0.31 to 0.71; [Analysis 1.6](#); [Figure 7](#)). Likewise, there was no significant difference in peak bilirubin levels (reported as subgroups according to method of delivery with 125 patients in the cesarean section group).

Figure 7. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.6 Phototherapy for hyperbilirubinaemia [days].

Respiratory outcomes

Use of surfactant in the first 48 hours of life

There were 24/75 infants in the V-DCC group and 29/75 in the DCC group who received surfactant in the first 48 hours of life after

leaving the delivery room (RR 0.83, 95% CI 0.54 to 1.28; [Analysis 1.7](#); [Figure 8](#)).

Figure 8. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.7 Use of surfactant in the first 48 hours of life.

Days of oxygen therapy

There was no difference in the number of days of oxygen therapy received between groups (MD 2.80 days, 95% CI -8.20 to 13.81; unpublished data).

Continuous positive airway pressure days

The study did not report the number of CPAP days.

Ventilation days

There was no significant difference in the median days of mechanical ventilation between groups ($P = 0.99$ as reported for

caesarean deliveries) or for the groups as a whole (unpublished data).

Oxygen requirement at 28 days

The study did not report oxygen requirement at 28 days.

Bronchopulmonary dysplasia as defined by respiratory support or oxygen requirement at 36 weeks' corrected gestational age (Outcome 1.8)

The number of cases with an oxygen requirement at 28 days was not reported, while there were 11 in the V-DCC group and 10 in the DCC group with an oxygen requirement at 36 weeks' corrected gestational age (RR 1.10, 95% CI 0.50 to 2.43; [Analysis 1.8](#); [Figure 9](#)).

Figure 9. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.8 Bronchopulmonary dysplasia.

Bronchopulmonary dysplasia at 36 weeks' postmenstrual age according to a physiological definition

The study did not report bronchopulmonary dysplasia at 36 weeks' postmenstrual age according to a physiological definition ([Walsh 2004](#)).

Other neonatal outcomes

Intraventricular haemorrhage (of any grade)

There was IVH (of any grade) in 12 of the infants in the V-DCC group and eight in the DCC group (RR 1.50, 95% CI 0.65 to 3.46; [Analysis 1.9](#); [Figure 10](#)).

Figure 10. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.9 Intraventricular haemorrhage (of any grade).

Severe intraventricular haemorrhage grade 3 or 4

There was severe IVH grade 3 or 4 in four infants in the V-DCC group and three in the DCC group (RR 1.33, 95% CI 0.31 to 5.75; [Analysis 1.10](#); [Figure 11](#)).

Figure 11. Forest plot of comparison: 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, outcome: 1.10 Severe intraventricular haemorrhage grade 3 or 4.

Periventricular leukomalacia

There was periventricular leukomalacia present in one infant in the V-DCC group and no infants in the DCC group (RR 3.00, 95% CI 0.12 to 72.49; [Analysis 1.11](#)).

Necrotizing enterocolitis Bell's stage 2 or greater

There was necrotizing enterocolitis (Bell's stage 2 or greater) in two infants in the V-DCC group and one infant in the DCC group (RR 2.00, 95% CI 0.19 to 21.59; [Analysis 1.12](#)).

Retinopathy all stages and stage 3 and greater

There was retinopathy of prematurity requiring treatment reported in four infants in the V-DCC group and two infants in the DCC group (RR 2.00, 95% CI 0.38 to 10.59; [Analysis 1.13](#)).

Sepsis

There was culture-positive sepsis reported in five infants in the V-DCC group and three infants in the DCC group (RR 1.67, 95% CI 0.41 to 6.73; [Analysis 1.14](#)).

Pharmacological treatment or surgical ligation for patent ductus arteriosus

Fourteen infants in the V-DCC group and 19 in the DCC group were treated for patent ductus arteriosus (RR 0.74, 95% CI 0.40 to 1.36; [Analysis 1.15](#)).

Four infants in each group had duct ligation performed (RR 1.0, 95% CI 0.26 to 3.85; [Analysis 1.16](#)).

Length of hospital stay

The study did not report length of hospital stay but length of neonatal stay from the unpublished data was similar in the V-DCC versus DCC groups (MD 0.05, 95% CI -12.02 to 12.13).

Over 90% of infants established respiration by the time of cord clamping. In a subgroup analysis of infants who did not establish respiration during DCC, whether vaginal or caesarean births, mortality, and severe IVH rates were not significantly different from infants who did establish breathing.

DISCUSSION

Summary of main results

Our search identified one trial where preterm infants undergoing DCC were randomized to a group receiving ventilation support before clamping (V-DCC group) compared to a group not receiving such support (DCC group) (see [Summary of findings for the main comparison](#)) ([Katheria 2016](#)).

There was no significant difference in mortality during neonatal admission between the groups. Likewise, there were no statistically significant differences in condition at birth, cardiovascular outcomes, haematological parameters (including bilirubin levels), respiratory outcomes, and other neonatal outcomes including IVH between the groups.

Overall completeness and applicability of evidence

The included study was the first RCT to provide respiratory support during delayed cord clamping ([Katheria 2016](#)). As such it provided preliminary evidence in relation to the study question

as to whether providing respiratory support to preterm infants before cord clamping is beneficial. The study reported in-hospital mortality but not neurodevelopmental outcomes. The study was not powered to detect differences in mortality and the wide CIs indicated lack of precision and included both potential benefit and potential harm. Therefore, we could draw no conclusions. Similar limitations applied to the interpretation of IVH rates and other neonatal outcomes. However, the study did indicate that the intervention was feasible and was carried out in a high percentage (95%) of eligible infants.

It is of interest that over 90% of study infants established respiration during the period of DCC and before cord clamping. This means that there was little separation between groups with regard to the effectiveness or otherwise of the intervention in promoting breathing movements during DCC. Many of the theoretical benefits of 'resuscitation with an intact cord' would be expected to occur in those infants who were not breathing on their own but commenced breathing after being given respiratory support. As there were few infants of this type, it remains to be seen if true benefits or harms exist with this approach and definite conclusions cannot be made.

We found no evidence of publication bias, as we found no unpublished studies.

Quality of the evidence

Although the study had an overall low risk of bias, the quality of the evidence for several of the key outcomes for the review was low to very low (GRADE) ([Katheria 2016](#)). This is because the study was underpowered to detect these outcomes. This means that, for important but relatively uncommon outcomes such as mortality and severe IVH, the estimates of effect lack precision with wide CIs encompassing the potential both for significant harm and significant benefit or indeed for no effect at all. For other outcomes such as blood transfusion and haematocrit, the quality of evidence was moderate (GRADE) and CIs were narrower. Of note, of the 150 infants in the study, approximately 10% were not displaying evidence of breathing and these were the infants most likely to be in need of respiratory support.

Potential biases in the review process

We found no apparent biases.

Agreements and disagreements with other studies or reviews

We found no other systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to evaluate the benefits or harms related to the provision of respiratory support before cord clamping in preterm infants. Potentially much larger studies will be needed to assess uncommon outcomes. For example, the mortality rate was 4% in the control group of the single included study. To detect a 30% reduction in mortality with 80% power at a significance level of p less than 0.05 would require 3280 infants in each group.

Implications for research

As the neonatal outcomes of most relevance to the review are relatively uncommon, adequately powered trials are needed for definitive conclusions. Neurodevelopmental outcomes (at a minimum of 18 months to two years and preferably longer) are regarded as very important for future studies and will be crucial in evaluating the usefulness or otherwise of the procedure. It will also be useful to report outcomes in the subgroup of infants not breathing during DCC. It is unknown how long attempts to establish respiration should be continued before clamping the cord, although, in the Cord Pilot Trial ([Duley 2018](#)), some infants were ventilated and received surfactant before clamping. Other trialists have proposed physiological cord clamping where cord clamping is delayed until respiration is established and the baby

monitored during the transitional period ([Hooper 2015](#)). Another potential approach in infants not breathing during DCC would be to undertake cord milking followed by clamping. This could be compared with a group of infants where clamping is carried out after a period of respiratory support. Future studies should continue to report potential adverse effects such as peak bilirubin levels, days of phototherapy, and incidence and any treatment for polycythaemia.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Katheria 2016

Methods	Single-centre randomized controlled trial stratified by gestational age and mode of delivery (caesarean section (83%) or vaginal birth (17%)). Sample size of 150 infants estimated to detect a 15% difference in peak haematocrit. A waiver of informed consent was obtained for women presenting in active labour.
Participants	Preterm infants 23 to 31 weeks 6 days' gestation delivered at Sharp Mary Birch Hospital in San Diego.
Interventions	Intervention group: V-DCC: 75 infants received 60 seconds of CPAP or PPV with room air provided by facemask with a T-piece resuscitator. Apnoeic infants were briefly stimulated and given PPV followed by CPAP when breathing was established. A colorimetric carbon dioxide detector used to assess adequacy of ventilation. Control group: DCC: 75 infants received 60 seconds of DCC. They were dried and, if apnoeic, received gentle stimulation.

Katheria 2016 (Continued)

Outcomes Primary outcome: maximum haematocrit in first 24 hours presented as mean and SD depending on the method of birthing (vaginal or caesarean).

Authors provided unpublished data that allowed group comparisons between V-DCC and DCC to be made. Inhospital mortality rate (1 of the primary outcomes of the current review) was likewise presented according to mode of birth. Condition at birth; measures of cardiovascular status; haematological and respiratory outcomes; and neonatal outcomes including intraventricular haemorrhage, blood transfusion, and duration of phototherapy were also reported by mode of birth. Event rates for categorical variables (e.g. mortality for the V-DCC and DCC groups as a whole) could be determined from the paper and continuous data (e.g. duration of phototherapy) was calculated from unpublished data.

Notes Study demonstrated the feasibility of the intervention. 95% of infants had at least 60 seconds of DCC. The majority of infants were delivered by caesarean section. Overall, 91% of participants established breathing before cord clamping. Subgroup analysis of mode of delivery and of infants who breathed during the procedure did not reveal significant differences.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified, computer generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not possible to blind personnel providing procedure at birth.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neonatal team blinded to group allocation at birth.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes presented.
Other bias	Low risk	None identified.

CPAP: continuous positive airway pressure; DCC: delayed cord clamping; PPV: positive pressure ventilation; SD: standard deviation; V-DCC: delayed cord clamping with ventilation support.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aladangady 2006	Control group randomized to early cord clamping.
Duley 2018	Control group randomized to immediate cord clamping.
Phillippos 2017	Observational study, non-randomized intervention.

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Study	Reason for exclusion
Winter 2017	Pilot feasibility study with no control group.

Characteristics of ongoing studies [ordered by study ID]

ABC study (ACTRN12615001026516)

Trial name or title	Provision of Breathing Support during Delayed Cord Clamping in Preterm Infants.
Methods	Randomized controlled intervention trial with parallel assignment and masking of outcome assessment.
Participants	<p>Inclusion criteria: preterm infants, < 31 weeks' gestation undergoing DCC (vaginal and caesarean births) deemed not to have established regular rhythmic breathing (chest wall movement) after 15 seconds of DCC.</p> <p>Exclusion criteria: known congenital abnormality, twin-to-twin transfusion syndrome, severe antenatal intrauterine growth restriction (estimated fetal weight < 10th customized centile), placental abruption, delivery of placenta and infant simultaneously (en caul), short umbilical cord, obstetrician refusal, declined antenatal consent.</p>
Interventions	<p>Intervention group: V-DCC. Breathing support in form of PPV or CPAP delivered by facemask and T-piece resuscitator. Infants will be randomized at 15 seconds of age once their breathing has been assessed. Breathing support will continue for 30 seconds while DCC is occurring (total of 50 seconds of DCC). Infants receiving breathing support will have a carbon dioxide calorimetric detection device inserted into the breathing circuit.</p> <p>Control group: DCC: no respiratory support before the cord is clamped at 50 seconds.</p>
Outcomes	<p>Primary outcome: red blood cell transfusion rate during the neonatal admission period.</p> <p>Secondary composite outcomes: chronic lung disease (respiratory support or use of supplemental oxygen at 36 weeks' corrected postnatal age), intraventricular haemorrhage (grade 3 or 4), and death (during the neonatal period).</p> <p>Other secondary outcomes: endotracheal intubation day 1, surfactant usage, admission temperature, echocardiographic assessment of transitional circulation, receipt of phototherapy, neonatal morbidity, length of hospital stay, and neurodevelopmental outcome at 2 years of age.</p>
Starting date	February 2016.
Contact information	elizabeth.nevill@cmdhb.org.nz ; mmeyer@middlemore.co.nz.
Notes	Australia and New Zealand Clinical Trials Registry: ACTRN12615001026516. Currently recruiting. Expected completion: June 2019.

te Pas 2016 (NTR6095)

Trial name or title	Stabilisation of Preterm Infants with Intact Umbilical Cord, Aeration, Breathing, then Clamping: a Feasibility Study.
Methods	Safety and feasibility study.
Participants	Vaginal births 26-35 weeks' gestation, planned recruitment of 15 infants.

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te Pas 2016 (NTR6095) (Continued)

Interventions	<p>Intervention group: infants will be placed on the Con-Cord table at the mother's bedside with monitoring and, with the umbilical cord intact, receive respiratory support according to local resuscitation guidelines.</p> <p>Control group: no respiratory support.</p>
Outcomes	Safety and applicability.
Starting date	Registered September 2016.
Contact information	NTR6095.
Notes	Part of a wider ABC project - the feasibility study has recently been completed and is to be followed by an effectiveness study, with the goal of subsequently performing a randomized trial.

VentFirst (NCT02742454)

Trial name or title	VentFirst: a Multicenter RCT of Assisted Ventilation during Delayed Cord Clamping for Extremely Preterm Infants.
Methods	<p>Multicentre, randomized controlled intervention trial with parallel assignment and masking of outcomes assessment.</p> <p>Collaborators: Brigham and Women's Hospital, Mayo Clinic, St Louis University, University of Colorado, Denver; Royal Alexandra Hospital Oregon Health and Science University, University of Calgary.</p>
Participants	<p>Inclusion criteria: 23 weeks and 0 days to 28 weeks and 6 days' gestation at delivery.</p> <p>Exclusion criteria: life-threatening condition of fetus (e.g. severe hydrops, lethal chromosomal abnormality, severe congenital malformation); suspected severe fetal anaemia; monochorionic or monoamniotic twins; multiple gestation greater than twins; decision made for comfort care only; medical emergency necessitating emergency delivery (e.g. complete placental abruption); obstetrician or neonatology concern for inappropriateness of the study intervention based on maternal or fetal factors.</p>
Interventions	<p>Intervention group: VentFirst (intervention) group will receive assisted ventilation (face mask, CPAP, or PPV) prior to cord clamping at 120 seconds. If the baby is not breathing well, PPV by face mask will be given at 30 seconds, if the baby is breathing well, CPAP by face mask will be given starting at 30 seconds.</p> <p>Control group: standard treatment group will receive DCC 30-60 seconds after birth, and assisted ventilation after cord clamping. If the infant is not breathing well, cord will be clamped at 30 seconds, and if the baby is breathing well, cord will be clamped at 60 seconds.</p>
Outcomes	<p>Primary outcome: intraventricular haemorrhage on head ultrasound 7-10 days after birth.</p> <p>Secondary outcomes: adverse events in delivery room (assessed at 1 hour after birth), adverse haematological and cardiovascular events (assessed within 24 hours of birth), adverse haematological and respiratory events (assessed within the first 10 days of birth), adverse prematurity-related events up to 36 weeks' postmenstrual age; and adverse finding on late head ultrasound (birth to 36 weeks' postmenstrual age).</p>
Starting date	June 2016.
Contact information	Amy K Camblos akc4c@virginia.edu.

VentFirst (NCT02742454) (Continued)

Notes

Planned enrolment of 940 infants ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02742454): NCT02742454). Currently recruiting at 6 of 8 sites. Expected study completion June 2023.

CPAP: continuous positive airway pressure; DCC: delayed cord clamping; PPV: positive pressure ventilation; V-DCC: delayed cord clamping with ventilation support.

DATA AND ANALYSES

Comparison 1. Respiratory support versus no respiratory support during delayed cord clamping in preterm infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality during neonatal admission	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.41, 6.73]
2 Need for intubation in delivery room	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.55, 1.21]
3 Inotropic support for hypotension	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.63, 2.49]
4 Peak haematocrit in first 24 hours	1	150	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.85, 2.25]
5 Blood transfusion during neonatal admission	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.70, 1.54]
6 Phototherapy for hyperbilirubinaemia	1	150	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.31, 0.71]
7 Use of surfactant in the first 48 hours of life	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.54, 1.28]
8 Bronchopulmonary dysplasia	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.50, 2.43]
9 Intraventricular haemorrhage (of any grade)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.65, 3.46]
10 Severe intraventricular haemorrhage grade 3 or 4	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.31, 5.75]
11 Periventricular leukomalacia	1	150	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.49]
12 Necrotizing enterocolitis $\geq$ Bell's stage 2	1	150	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.59]
13 Retinopathy of prematurity requiring treatment	1	150	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.38, 10.59]
14 Sepsis	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.41, 6.73]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Pharmacological treatment for patent ductus arteriosus	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.40, 1.36]
16 Surgical ligation for patent ductus arteriosus	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.26, 3.85]

Analysis 1.1. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 1 Mortality during neonatal admission.

Analysis 1.2. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 2 Need for intubation in delivery room.

Analysis 1.3. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 3 Inotropic support for hypotension.

Analysis 1.4. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 4 Peak haematocrit in first 24 hours.

Analysis 1.5. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 5 Blood transfusion during neonatal admission.

Analysis 1.6. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 6 Phototherapy for hyperbilirubinaemia.

Analysis 1.7. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 7 Use of surfactant in the first 48 hours of life.

Analysis 1.8. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 8 Bronchopulmonary dysplasia.

Analysis 1.9. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 9 Intraventricular haemorrhage (of any grade).

Analysis 1.10. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 10 Severe intraventricular haemorrhage grade 3 or 4.

Analysis 1.11. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 11 Periventricular leukomalacia.

Analysis 1.12. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 12 Necrotizing enterocolitis ≥ Bell's stage 2.

Analysis 1.13. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 13 Retinopathy of prematurity requiring treatment.

Analysis 1.14. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 14 Sepsis.

Analysis 1.15. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 15 Pharmacological treatment for patent ductus arteriosus.

Analysis 1.16. Comparison 1 Respiratory support versus no respiratory support during delayed cord clamping in preterm infants, Outcome 16 Surgical ligation for patent ductus arteriosus.

APPENDICES

Appendix 1. Search strategies

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infant* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomised [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 infant* 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 infant* 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)

Appendix 2. 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 randomization, 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. We resolved any disagreement by discussion. We added this information to the table Characteristics of included studies. We evaluated the following issues and entered the findings into the risk of bias table.

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

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

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk.

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

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

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk.

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 categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorized the methods as:

- low risk, high risk, or unclear risk for participants;
- low risk, high risk, or unclear risk for personnel.

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 categorized the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorized the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors;
- unclear risk for outcome assessors.

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 were reported, the numbers included in the analysis at each stage (compared with the total randomized 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 categorized the methods as:

- low risk (< 20% missing data);
- high risk ($\geq$ 20% missing data);
- unclear risk.

Selective reporting bias. Are reports of the study free of 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:

- low risk (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review were reported);
- high risk (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified outcomes of interest and were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk.

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

- low risk;
- high risk;
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the study design and protocol ([Meyer 2017](#)).

MM extracted the data and MW checked the entries.

MM and MW evaluated the quality of evidence according to GRADE, and evaluated the risk of bias.

MM wrote the primary draft of the review and all authors approved the content.

DECLARATIONS OF INTEREST

Two of the review authors (MM and EN) are investigators for the ABC study (see [Characteristics of ongoing studies](#) table).

MW: has no conflict of interest to report.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The included study presented results for caesarean and vaginal births separately. It was not our intention to have mode of birth as a separate subgroup. Summary results for categorical outcomes could be generated from the original article. Results for continuous variables (e.g. haematocrit and days of phototherapy) were generated from unpublished data made available by the authors.

INDEX TERMS

Medical Subject Headings (MeSH)

*Umbilical Cord; Blood Transfusion [statistics & numerical data]; Cerebral Intraventricular Hemorrhage [epidemiology]; Constriction; Continuous Positive Airway Pressure [methods] [mortality]; Hematocrit; Hospital Mortality; Hyperbilirubinemia [therapy]; Hypotension [therapy]; Infant, Premature; Phototherapy [statistics & numerical data]; Positive-Pressure Respiration [*methods] [mortality]

MeSH check words

Humans; Infant, Newborn