Study Protocol

The ABC Study ‘Assisted breathing before cord clamping’

Effect of breathing support during delayed cord clamping (DCC) for very preterm infants: A randomised controlled trial

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Version 11: 5 March 2018:
• Addition of ABC Theatre Procedure Protocol – Appendix 1 p13
• Secondary outcomes: Patient ductus arteriosus added p5
• Echocardiogram clarification p9
• DSMC clarification p10
**Background**

Infants born at <31 week gestation are the most vulnerable patients in the neonatal unit and often receive red blood cell (RBC) transfusions during their initial hospital stay \(^{[1-4]}\). Transfusion is not without cost, and potential adverse long-term outcomes \(^{[2,5-7]}\). The very preterm population is known to be at risk for morbidities including necrotising enterocolitis (NEC), chronic lung disease (CLD) and intraventricular haemorrhage (IVH) \(^{[5,8-11]}\). RBC transfusions have been implicated in contributing to these morbidities, and may adversely effect long term outcomes for these already vulnerable infants \(^{[2,6,10]}\).

Delayed cord clamping (DCC) facilitates placental transfusion (PTF) with the important benefit of increasing haemoglobin levels and thereby reducing the need for RBC transfusions \(^{[9,11,12]}\). The safety and efficacy of DCC for preterm infants has been reported and as such, is recommended as a safe and achievable standard practice \(^{[5,13,8,14-18]}\). Recent attention has focused on improved haemodynamic stability; improved cerebral oxygenation and cerebral blood flow following DCC, reducing the risk for IVH. This could improve long-term neurodevelopmental outcomes \(^{[11,13,18,19]}\). DCC has been adopted as standard practice for preterm infants in our unit since 2010\(^{[20]}\). An audit of our results showed that those infants who did not establish regular respirations during DCC had worse outcomes than those that did breathe. There were significantly lower day one haemoglobin levels, increased rates of CLD and severe IVH \(^{[20]}\). In term infants, breathing during DCC has been shown to increase PTF \(^{[21]}\).

Bhatt and colleagues reported ventilation prior to clamping of the cord to be an important factor in improving cardiovascular stability in a study of preterm lambs and this could be important in preventing IVH \(^{[13,22]}\). In addition other reports have shown a clear association between reduced transfusion rates and IVH \(^{[2,3]}\).

Provision of breathing support during DCC may facilitate optimal PTF, reduce the need for RBC transfusion and result in a more stable neonatal transitional circulation. This may improve neurodevelopmental outcomes for preterm infants born <31 week gestation. To date, no clinical studies, have reported the effect of breathing support during DCC. The possible clinical and economic benefits of adding breathing support during transition warrants further research. This
study will evaluate the effect of breathing support on outcomes for those infants that fail to establish sustained spontaneous breathing while receiving DCC.

**Study Aim:** The aim of this study is to evaluate the effect of breathing support on placental transfusion and cardiovascular stabilisation during delayed cord clamping, in preterm infant’s < 31 weeks gestation.

**Methods and Design**

**Trial Design:** Prospective single centre randomised blinded controlled trial. Preterm infants born <31 week gestation will be recruited over an estimated 3 year period. Infants will be randomised to receive standard treatment (position, thermal wrap) or breathing support in addition to standard treatment during 50 sec delayed cord clamping. Infants will remain in the study until discharge from hospital.

**Sample size:**
Our observational data indicated that 60% of infants that received DCC and did not breathe received a RBC transfusion. Aiming for a 50% relative reduction in RBC transfusion, would require 120 infants whose primary outcome can be assessed. This would give the study 85% power at a significance level of 0.05. For a secondary composite outcome of death, CLD or severe IVH, the sample size would allow a 36% difference in outcome to be detected (80% power, significance 0.05; assuming the proportion of infants with a composite endpoint will be 58%). We plan to randomise 60 infants to each group. Based on mortality of 15% this will allow for the loss of 10 infants per group and result in 50 infants per group whose primary outcome can be determined. Our average admission rate is 70 <31 week infants per year, and estimating that 50% of infants do not breathe regularly by 15secs of age, the length of this study will be approximately 3 years.

**Trial entry and randomisation**
Parents will be given a written information sheet about the study by a study researcher before labour where possible. In cases where active labour is in progress; and consent before birth is not possible, deferred consent for study entry is proposed. Eligible infants that receive DCC will be randomised at 15 sec of age once the breathing has been assessed.
Study groups and management: A standard treatment arm will be compared to an intervention arm. Standard treatment consists of: position (placed on their back, head in neutral position), and thermal wrap during 50sec delayed cord clamping.

Interventional treatment: In addition to the standard treatment above, breathing support in the form of intermittent positive pressure ventilation (IPPV) and continuous positive airway pressure (CPAP) delivered by mask and pressure controlled device.

Randomisation: Randomisation will occur via sequentially numbered opaque sealed envelopes. A card folded within the envelope will state whether the infant is to receive standard treatment (no breathing support) or breathing support (intervention) during delayed cord clamping. These cards will be attached to the data collection sheet. The infants study number will be documented in the clinical notes. Groups will be stratified into <26, ≥26-27.6, ≥28-30.6 week gestation.

Blinding: The attending resuscitation team will not disclose to clinicians whether infants received respiratory support during DCC or not.

Outcome Measures

Primary outcome: RBC transfusion rates, during the neonatal admission. Current transfusion guideline will remain unchanged during the planned study period.

Secondary outcomes:

• Endotracheal intubation (ETT) day one, surfactant usage
• Temperature after DCC (5min of age), admission temperature
• Transitional circulation assessed, on the basis of echocardiogram performed < 24hours of age (within first 6 – 12 hours if possible); including SVC flow, RVO, PDA, inotropes received
• Phototherapy received
• Length and type of ventilation support
• Chronic lung disease defined as respiratory support at 36 weeks corrected gestational age, home oxygen
• IVH (grades 3&4), defined by ANZNN coding criteria within first 24hours if possible, day 5 and day 28 cranial ultrasound.
• Necrotising enterocolitis (NEC), defined by modified Bells stage 2 or higher.
• Retinopathy of prematurity (ROP) requiring laser therapy
• Late onset sepsis (LOS) defined by positive blood culture or CSF after 48 hours
• Death during neonatal admission
• Length of hospital stay in days
• Patent ductus arteriosus (PDA), defined as 2D diameter >1.5mm with Left heart enlargement at ≥ day 14
• Neurodevelopmental outcome at 2yr of age (for infants ≤ 29 week gestation).

Inclusion and Exclusion Criteria

**Inclusion:** Infants born <31 week gestation and undergoing DCC (born by vaginal or caesarean section) and deemed not to have regular rhythmic breathing (chest wall movement) after 15sec of DCC. (See below for ethical consideration).

**Exclusion:** Infants born ≥ 31 week gestation, known congenital abnormality, twin-to-twin transfusion syndrome, severe antenatal intrauterine growth restriction (estimated fetal weight <10th customised centile), placental abruption, delivery of placenta and infant simultaneously (en caul), short umbilical cord, obstetrician refusal, declined antenatal consent. Infants transferred to another hospital, for ongoing care (most of whom will receive surgery) will be excluded from the analysis of the primary outcome to avoid the problem of differing blood transfusion protocols.

Intervention

1. Obtained consent before birth where possible
2. Sealed randomisation envelopes will be kept in the locked research office.
3. The numbered envelopes will be in a designated study box having compartments for the stratified (≤26, 26.1-27.6 and ≥28-30.6 week gestation) groups.
4. The neonatal resuscitation team leader will take a numbered sealed envelope (containing a double folded sticky label containing a randomisation number) from the appropriate stratified group to the anticipated delivery of < 31week infants.
5. Randomisation will take place at 15sec of age once the infant is covered in a thermal wrap, placed in a neutral position and the breathing has been assessed.
6. Infants who are apnoeic or do not have sustained breathing effort will be randomised to either receive the planned intervention or standard practice. (Infants that have sustained spontaneous breathing effort at birth and during DCC will not be randomised to receive the
intervention and, will not enter the study). Infants who initially establish respiration and then became apnoeic after 15 sec of age will receive standard treatment.

7. Infants will be positioned at the level of the maternal thigh (on a sterile flat surface) for caesarean section deliveries and at the level of the introitus on the bed for normal births.

8. Standard treatment (control group), consists of placing the infant in neutral breathing position and using a thermal wrap.

9. In cases where the umbilical cord is too short to perform the intervention, standard treatment will be given.

10. The intervention (study group) consists of positive pressure ventilation (PPV) or continuous positive airway pressure (CPAP) commencing at 20sec of age and continuing for a further 30sec (infants will therefore receive 50sec of DCC). Respiratory support will take the form of CPAP or PPV delivered by mask and regulated pressure device. Recommended ILCOR resuscitation guidelines for preterm infants will be adhered to. A paediatric colorimetric CO₂ detector (PEDICAP) will be attached between the mask and inspiratory circuit to ascertain effective ventilation. DCC will be timed using the Apgar score timer and clamping will occur at 50sec. Once the cord is cut the infant will be transferred to a radiant warmer and receive ongoing standard management.

11. As per standard practice, infants requiring ongoing CPAP will be commenced on nasal prong CPAP, have a thermistor applied for skin servo and have heart rate and oxygen saturation monitoring prior to being transported to the neonatal unit on a radiant warmer with an uninterrupted power supply.

12. For those infants born flaccid, cyanosed or pale and shocked the attending team may elect to perform cord milking (current standard practice); these infants will not be included in the study.

13. Apart from the initiation of ILCOR guidelines during DCC in the intervention arm, standard neonatal treatment will apply to all infants enrolled in the study. No additional testing or procedures will be required.

14. The randomisation number (sticky label) with randomised intervention will be placed on the data capture sheet (completed at delivery). The birth record will only contain The ABC Study number. Data capture sheets will be placed in a designated folder in the locked research office by the resuscitation team leader so as not to disclose the intervention received.
15. In cases where antenatal consent could not be obtained and parents decline consent for data collection, the initial data capture sheet will be discarded.
The ABC Study: Flow diagram

Assess Eligibility

- <31 week gestation
- Caesarean section and vaginal births

Assess entry to trial at birth
n=250

Exclusion Criteria
- >31 week gestation
- Declined antenatal consent
- Known congenital abnormality
- Twin-to-twin transfusion syndrome
- Severe antenatal IUGR
- Placental abruption
- En caul delivery
- Short umbilical cord
- Obstetrician refusal

Flaccid, pale and shocked
Consider cord milking

Sustained spontaneous
breathing from birth to 15sec
(regular chest wall movement)

Does not qualify for randomisation

Estimated n=120
No breathing or irregular breathing

RANDOMISE
At 15 sec of age

n=60 Allocated to Standard treatment: control group
Position, thermal wrap
DCC 50sec

n=60 Allocated to Intervention: breathing support during DCC
PPV or CPAP delivered by Neopuff From 20—50sec

Consent obtained
And eligible for assessment of primary outcome

Declared collection of data
EXCLUDED

ANALYSIS PER ITT
n=60 per group

ANALYSIS PER PROTOCOL
n=50 per group
**Data collection**

Information will be entered on data capture sheets by the attending resuscitation team; ongoing data collection will be done by the research team. Data sheets will be kept in a locked research office, entered electronic data (data base) will be password protected. Data collection will encompass the following:

- **Maternal characteristics:** Ethnicity, age, delivery method, multiples, antenatal steroids received (completed, incomplete, complete, 7 days, none), magnesium sulphate received within 6 hours of birth, pregnancy complications including: preterm labour, prolonged rupture of membranes, antepartum haemorrhage, pregnancy induced hypertension, chorioamnionitis (placental histology), antibiotics received in labour, intrauterine growth restriction (<10th percentile of estimated fetal weight).

- **Infant characteristics:** Ethnicity, Gender, gestation (weeks), birth weight (g), Intrauterine growth restriction (birth weight <10% percentile).

- **Transition data:** procedure received, palpated heart rate at birth (if possible), DCC total time in sec, Apgar score at 1 and 5 min, resuscitation received, intubation in delivery room, oxygen saturation (first reading, 5 and 10 min, 30 min and 1 hour of age), highest percentage oxygen received in delivery room, temperature after 50 sec DCC (5 min of age), admission temperature, worse base deficit on admission.

- **Respiratory data:** Maximum oxygen received in first 6 hrs of life, total time (hrs) oxygen received in first 6 hours, oxygen received at each time point for first 6 hrs, Surfactant received, ventilated days, CPAP days, high flow nasal cannula (HFNC) days, low flow oxygen days, CLD (respiratory support or oxygen at 36 weeks), home oxygen.

- **Haemodynamic data:** echocardiogram < 24 hours of age (within 6-12 hr of age if possible) evaluating cardiovascular stability; including need for inotropic support, haemoglobin day 1 to 77 (weekly intervals as per standard neonatal blood sampling). RBC transfusion received, day of first RBC transfusion, number transfusions received, first transfusion age (days), erythropoietin received (dose and days of treatment), PDA and treatment received. The standard unit practice to evaluate PDA, is to perform an echocardiogram on day 3 and 14. Phototherapy received, number of days received and maximum serum bilirubin.

- **Neonatal outcome data:** IVH grade 1&2, IVH grade 3&4 or periventricular leukomalacia detected on cranial USS on day 1 (6-12 hours of age if possible), and day 5, day 28 and term (as current standard practice), neurodevelopmental outcome at 2 yr of age as assessed.
(Bayley III) at Neonatal Clinic (current standard practice for ≤29weeks), NEC (Bell stage 2 or more; ± surgery), surgery received, transferred to another DHB for surgery, retinopathy of prematurity (ROP) treated with laser therapy, sepsis (<48hrs of age), LOS (sepsis >48hrs of age), death before discharge, breast feeding at discharge.

- Length of neonatal admission in days.

**Potential Risks**

Potential compromise to the sterile surgical field will be minimised by the use of sterile Neopuff circuits, sterile masks, PEDICAP's and sterile thermal wrap (current practice) in operating theatres. The neonatal team attending caesarean section deliveries will maintain sterile technique by scrubbing and gowning for the procedure. During the procedure the neonatal resuscitation team leader will communicate clearly with obstetric and theatre staff to enable correct implementation of the procedure and will abandon the procedure in cases where the obstetric team advise potential compromise to the mother. The neonatal resuscitation team leader will take responsibility to consider cord milking for infants born flaccid pale and shocked that need immediate resuscitation; these infants will not be enrolled in the study but record kept of the number of such cases. Numbers will also be recorded of the infants that breathed initially (did not qualify for the intervention) and became apnoeic later.

The DSMC will be notified with the following adverse events as stipulated in DSMC terms of reference:

**Serious Adverse Events (SAE)**

1. Death in the first 7 days of life
2. Death secondary to birth asphyxia – not able to be resuscitated at birth
3. Any serious adverse events – that the ABC Trial Steering Committee believes should be referred to the Independent Safety Monitoring Committee

**Adverse Events (AEs) for notification (6 monthly as part of DSMC report).**

1. (Grade 3 or 4) intraventricular haemorrhage (IVH)
2. Polycythaemia in the first 24hours of life (haematocrit ≥65%) requiring treatment
3. Pneumothorax in the first 24hours of life requiring a chest drain
4. Postpartum maternal infection, requiring more than 48hrs of antibiotics in the first 7 days’ post-delivery.
5. In addition, any compromise to maternal health will be reported.
The following will be reported to the DSMC by arms and stratum on all discharged participants (as per template provided by DSMC) and be part of 6 monthly reports:

a. Temperature after DCC;
b. Temperature on admission;
c. Respiratory support at 36 weeks;
d. Home oxygen;
e. IVH 3 and 4;
f. Blood transfusions

Ethical considerations

In cases of established labour, when antenatal consent is not possible, we propose a consideration of deferred consent and to gain consent for collection of outcome data. The provision of respiratory support during delayed cord clamping is a low risk intervention and possibly of lower risk than not providing any breathing support.

Northern A Health and Disability Ethics Committee (HDEC) full review:
HDEC registration number: 15/NTA/146
Approval granted – deferred consent: 27 June 2016 (15/NTA/146AM 02)

Counties Manukau Maaori Ethics approval 29/10/15
Counties Manukau Women’s Health Research approval 30/11/15
Consultation and approval received from CMH:

- Obstetric SMO team – 30/11/15
- LMC Access Holders – 17/11/15
- Assessment and Birthing Midwifery Team-7/12/15
- Patient Whanau Centred Care Consumer Council-14/12/15
- CMH Legal Office-22 March 2016
Statistical analysis

Analysis will be carried out on an intention to treat (ITT) basis as well as per protocol analysis. IBM statistics for data analysis version 22.0 will be used. The primary outcome will be analysed using Chi-Square test by RCT group, and multiple logistic regression adjusted for infant and maternal clinical characteristics. The other binary outcomes will be analysed by using a similar approach. The continuous outcomes will be analysed by using two-sample t-test and non-parametric methods as appropriate.

Trial registration: Australian New Zealand Clinical Trials Registry number:

ACTRN: 12615001026516

Acknowledgements:

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References


15. Raju TNK. Don’t rush to cut the cord: New recommendations call for delaying cord clamping in preterm infants. 2013; AAP News; 34; 17. [DOI: 10.1542/aapnews.2-13344-17]


21. Redmond A, Isana S. Relation of onset of respiration to placental transfusion. The Lancet 1965; Feb (6); 284285.

## Appendix 1: ABC Theatre Procedure Protocol

### What to take to Theatre?
- ABC theatre pack from box in locked research office
- Stratified Randomisation card
- Thermometer
- ABC Clipboard

### Neopuff & $O_2$ Blender
- Portable Neopuff stand + $O_2$ Blender → in theatre 5 anteroom
- Connect to pendant gas outlets; closest to the mothers’ feet
- Set $O_2$ Blender at 30% Oxygen and flow meter at 10L
- Set Neopuff pressure as 20/5
- Please place device back in anteroom 5 after the procedure

### Preparation
- Resuscitation team leader (RTL) performs 4 min surgical scrub
- Hat, mask + sterile gown and gloves
- Adhere to sterile technique
- **Assistant**: Opens equipment into blue sterile draped cot → sterile Neopuff circuit, sterile mask, Pedicap, plastic wrap and sterile single packed warm towel
- **RTL** prepares circuit (including Pedicap) and passes tip to be connected to Neopuff → tests pressures → secures sterile circuit with towel clip onto sterile field (mothers’ legs)
- Fold warm sterile towel in a square + open sterile wrap completely + place on top of towel; fold sides up → sides of wrap must not hang down when towel is lifted

### Time Keeping
- 15 secs timer attached to Neopuff stand (counts down + alarms) and Apgar Score timer will be activated simultaneously
- Once RTL announces ‘baby out’ assistant 1 immediately starts 15 secs count down timer on Neopuff stand and assistant 2 starts Apgar Score timer in anteroom
- Assistant 1 opens the Randomisation envelope only if instructed to do so, at 15 secs; and announces 50 secs time point.

### Randomisation Procedure
- Clear communication with Obstetric and Anesthetic staff is vital
- Oxytocin must be given after completion of 50secs DCC
- Discuss planned procedure, stand back until uterus is open → place sterile towel with plastic wrap close to incision; on maternal thigh → open wrap completely → surgeon delivers baby onto plastic wrap
- RTL announces, ‘Baby Out’.
- RTL applies the thermal wrap and ensures a neutral breathing position + palpates cord for 6 sec.
- 15 secs → timer alarm → evaluate breathing effort and decide if eligible to randomize → announce *open* or *baby breathing*
• Assistant 1 opens envelope when RTL say ‘open’ + announces white / blue.
• White indicates standard care and blue indicated intervention/breathing support
• RTL performs allocated procedure → surgeon clamps and cuts the cord at 50 secs → RTL places baby in cot + transfers to heat table
• Attending NICU team follow standard procedure for stabilization + transport to NICU
• RTL requests Cord FBC and Cord Gas and placenta histology if chorioamnionitis is possible
• Complete ABC data sheet and birth record
• Attending staff will not disclose the allocated intervention to others
• Obtain consent for collection of outcome data in cases where antenatal consent was not possible; within 24 hrs of birth.