Neonatal Resuscitation with an Intact Cord: A Randomized Clinical Trial

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Objective To assess whether providing ventilation during delayed cord clamping (V-DCC) increases placental transfusion compared with delayed cord clamping alone (DCC only).

Study design Inborn premature infants ($23^{0/7}$-$31^{6/7}$ weeks' gestational age) were randomized to receive at least 60 seconds of V-DCC (initial continuous positive airway pressure) with addition of positive pressure ventilation if needed) or without assisted ventilation (DCC only). For the DCC-only group, infants were dried and stimulated by gently rubbing the back if apneic. The primary outcome was the peak hematocrit in the first 24 hours of life. Delivery room outcomes were analyzed from video recordings and a data acquisition system. Hemodynamic measurements were performed with the use of functional echocardiography, near-infrared spectroscopy, and electrical cardiometry.

Results There was no difference in the primary outcome of peak hematocrit in the first 24 hours of life. The onset of breathing was similar between both groups (25 ± 20 and 27 ± 28 seconds, $P = .627$); however, infants receiving DCC received a greater duration of stimulation than V-DCC (41 ± 19 and 20 ± 21 seconds $P = .002$). There were no differences in delivery room interventions, early hemodynamics (cerebral oxygenation by near-infrared spectroscopy, cardiac output and stroke volume by electrical cardiometry, or superior vena cava flow by of functional echocardiography), or neonatal outcomes.

Conclusions V-DCC was feasible but did not lead to any measurable clinical improvements immediately after delivery or reduce subsequent neonatal morbidity. Caretakers should consider providing adequate stimulation before cord clamping. *(J Pediatr 2016;178:75-80).*

Trial registration ClinicalTrials.gov: NCT02231411.

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Recently, the International Liaison Committee on Resuscitation (ILCOR) recommended delayed cord clamping (DCC) for longer than 30 seconds in both term and premature infants who do not require resuscitation.[1] DCC in preterm infants has been associated with a reduction in intraventricular hemorrhage (IVH) and less need for blood transfusions. A recent Cochrane meta-analysis of 10 randomized controlled trials of DCC compared with immediate cord clamping reported a lower incidence of IVH in those receiving DCC (35/260 [13%]) vs controls (56/279 [20%]), or a 35% relative decrease.[2]

This evidence and the ILCOR statement should have changed the standard of care for all preterm deliveries by eliminating immediate cord clamping. Interestingly, in the largest published meta-analysis, DCC reduced overall IVH without a significant reduction in severe (grade 3 or 4) IVH.[2] One possibility is that the volume of placental transfusion may be diminished during cesarean delivery, which is the mode of delivery for approximately 70% of premature infants.[3] Trials that compared DCC with immediate cord clamping found no difference in hematocrit in infants delivered by cesarean.[4-6] The statement from the American Congress of Obstetricians and Gynecologists acknowledges that there are limited data to determine whether DCC performed during cesarean delivery can improve placental transfusion.[7] We have shown previously that a placental transfusion with DCC is inferior to umbilical cord milking at cesarean but not during vaginal delivery.[8]

An important consideration is whether resuscitation interventions would be beneficial during a delayed placental transfusion, perhaps by increasing the accepting reservoir for placental blood through decreasing pulmonary vascular resistance. We hypothesized that the provision of early continuous positive airway pressure (CPAP)

CO	Cardiac output
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
DCC	Delayed cord clamping
FiO_2	Fraction of inspired oxygen
ILCOR	International Liaison Committee on Resuscitation
IVH	Intraventricular hemorrhage
NIRS	Near-infrared spectroscopy
PPV	Positive pressure ventilation
SV	Stroke volume
V-DCC	Ventilation during delayed cord clamping

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during DCC, with addition of positive pressure ventilation (PPV) if the infant was apneic, would increase placental transfusion at cesarean delivery as determined by an increased hematocrit. In addition, we hypothesized that such an approach would improve circulatory hemodynamics, such as cerebral oxygenation and systemic blood flow measured by echocardiography. Unlike previous trials of DCC that excluded infants who needed resuscitation, we encouraged inclusion of these infants to ensure the most compromised infants received DCC. We also stratified and randomized infants separately after vaginal delivery, because the effects of ventilation in this subgroup are unknown.

Methods

This was a randomized, blinded controlled trial conducted at Sharp Mary Birch Hospital for Women & Newborns and approved by the institutional review board (ClinicalTrials.gov: NCT02231411). Pregnant women who were dated by their earliest ultrasound scan at <32 weeks' gestation were approached for consent. Antenatal consent was not always practical because it would potentially exclude the sickest newborns born to women unable to provide consent before emergent preterm delivery. DCC and providing CPAP or PPV were both separate but standard treatments in the first minute of life and were not thought to add risk because they are provided routinely after delivery. The World Health Organization has recommended if there is experience in providing ventilation without cutting the umbilical cord, ventilation can be initiated before cord cutting.[9] Our obstetricians already were providing DCC routinely and were aware that they could override the protocol and perform early clamping if necessary. Therefore, we requested that the institutional review board grant a deferred waiver of informed consent based on the inability to conduct the trial without a waiver and minimal risk of either intervention.

Parents were approached for antenatal consent if there was adequate time and opportunity (ie, not in active labor) for consent before delivery. If antenatal consent was not possible, parents were notified of the intervention by the obstetrician or research team at delivery and were approached immediately after birth to provide written consent to enroll their newborn and for continued data collection and study-related procedures (eg, echocardiograms, additional monitoring). If a parent did not want to enroll his or her child in the study, we removed the subject from our study. Exclusion criteria included monochorionic multiples, placenta previa, concern for abruption, Rh sensitization, hydrops, and congenital anomalies. If at the time of delivery, an abruption occurred, the cord was clamped immediately and cut, and the subject was removed from the trial.

Infants were randomized by opaque, sealed envelopes immediately before delivery. A computer-generated randomization table was used. Subjects were stratified by gestational age and mode of delivery (23-$27^{6/7}$ or 28-$31^{6/7}$ weeks) to ensure that an equal number of infants born at <28 weeks' gestation were in each arm. The research team opened the randomization cards when notified of a subject's impending birth, reviewed the protocol with the obstetricians, and recorded the time from delivery until the clamping and cutting of the umbilical cord in both groups.

Research staff recorded the type of ventilation (CPAP and/or PPV) and the time elapsed from when the infant was delivered until the time the umbilical cord was clamped. The time to first breath (chest movement) and/or cry was recorded.

When feasible, video recordings were obtained by fixed cameras (GoPro, Cardiff-by-the-Sea, California) affixed to the LifeStart Trolley (Inditherm Medical, Rotherham, United Kingdom). The camera was positioned as another method to determine whether the baby was breathing. DCC was performed by the obstetric team by having the delivering obstetrician place the infant on the LifeStart Trolley (with a chemical heat mattress placed on top) covered in a sterile drape. The bed was lowered to at least the level of the uterine incision at cesarean delivery or below the mother's introitus at vaginal delivery. A neonatal provider (typically a neonatal nurse practitioner or member of the research team) was draped in sterile gown and handed a facemask connected to a T-piece after the infant was born to avoid contamination of the field. If randomized to ventilation during delayed cord clamping (V-DCC), the infant was dried briefly and if apneic (no initial gasping or crying efforts) was stimulated briefly by rubbing the infant's back with warm dry towels. The provider then placed the CPAP mask on the infant and delivered a CPAP of 5 cm H_2O with a NeoPuff Infant Resuscitator (Fisher and Paykel, Auckland, New Zealand) at an fraction of inspired oxygen (FiO_2) of 0.21. The mask and T-piece were connected to a colorimetric carbon dioxide (CO_2) detector (NeoStatCO_2; Mercury Medical, Clearwater, Florida). The time that the CO_2 detector changed color was called out by the provider and recorded by the research staff. If the infant was still apneic, PPV (peak inspiratory pressure set at 20 cm H_2O) was provided. Lack of color change during PPV demonstrated to the provider that the airway potentially was obstructed, the pressure was insufficient to expand the lungs, that there was excessive air leak, or there was no or inadequate pulmonary blood flow. If there was no color change, the provider either repositioned and adjusted the mask and airway and could deliver prolonged inflations (up to 5 seconds) and repeat if needed. Once ventilation was established, the infant then remained on CPAP of 5 cm H_2O until the cord was clamped.

If the infant was randomized to DCC only, the infant was dried and stimulated (by gently rubbing the back with warm sterile towels) if apneic, until the onset of breathing. The occurrence and duration of stimulation and the onset of breathing were recorded by the research team and confirmed by video recordings when available. Once the cord was clamped and cut, the infant was handed through a window in the resuscitation suite, where the neonatal team (blinded to the intervention) resuscitated the infant according to our unit's protocol, which was that all infants <32 weeks initially received CPAP (at 5 cm H_2O) or PPV with positive end-expiratory pressure