



Delayed Cord Clamping in Newborns Born at Term at Risk for Resuscitation: A Feasibility Randomized Clinical Trial

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Infants may benefit if resuscitation could be provided with an intact umbilical cord. Infants identified at risk for resuscitation were randomized to 1- or 5-minute cord clamping. The 5-minute group had greater cerebral oxygenation and blood pressure. Studies are needed to determine whether this translates into improved outcomes. (*J Pediatr* 2017;187:313-7).

Trial registration [ClinicalTrials.gov: NCT02827409](https://clinicaltrials.gov/ct2/show/study/NCT02827409).

Delayed cord clamping (DCC) in newborns born at term has not been shown to affect neonatal death or morbidity outcomes.^{1,2} Because of the complexity of providing supportive interventions with the umbilical cord intact, most subjects in published studies have not required resuscitation. This has prompted the American Academy of Pediatrics and the International Liaison Committee on Resuscitation to acknowledge that there is insufficient evidence to recommend an approach to cord clamping for newborns who require resuscitation at birth.^{3,4}

The timing of “late” cord clamping is variable, ranging from 30 seconds to 5 minutes or to when the cord stops pulsating. Currently, infants requiring resuscitation do not benefit from DCC because of the practice of removing the infant from the mother to perform resuscitation. The primary driver of cutting the cord of an unstable infant is the determined need for resuscitation intervention. Recently, we and others have demonstrated the benefits of using a bedside trolley (LifeStart; Inditherm Medical, Rotherham, United Kingdom) that allows resuscitation interventions to be initiated while the cord remains intact for 60-90 seconds.⁵⁻⁷ We have shown that DCC for 5 minutes improves cardiac output in healthy infants born at term after vaginal birth.⁸ Infants at risk for resuscitation may benefit from extended placental transfusion by increased blood volume and potentially improved outcomes. The establishment of ventilation before cord clamping facilitates the transition from fetal circulation and gas exchange in the lung, which is critical for adequate oxygenation of the brain.⁹ We hypothesized that in infants born at term at risk for resuscitation, 5-minute DCC with the use of resuscitation interventions compared with 1-minute DCC (or sooner if requiring resuscitation) would improve transition at birth and increase cerebral tissue oxygen saturation (StO₂) as measured by near-infrared spectroscopy at 12 hours of life.

Methods

We conducted a randomized controlled trial ([ClinicalTrials.gov: NCT02827409](https://clinicaltrials.gov/ct2/show/study/NCT02827409)) of vaginally delivered neonates ≥ 37 weeks' gestational age who required the attendance of a neonatal provider (neonatal nurse practitioner, advance life support nurse, and/or physician) because of an at-risk delivery. The institutional review board of Sharp Health Care approved the study. At our institution, the criteria for the attendance of a neonatal provider included infants with a fetal heart rate (HR) tracing showing minimal-absent variability, recurrent fetal HR decelerations, prolonged tachycardia or bradycardia, shoulder dystocia, fetal malpresentation, vacuum- or forceps-assisted vaginal delivery, and meconium-stained amniotic fluid. Exclusion criteria were planned or progression toward cesarean delivery, multiple gestations, or known congenital anomalies ([Figure 1](https://www.jpeds.com); available at www.jpeds.com). If there was a placental abruption, nonreducible nuchal cord or a cord accident, or avulsion at the time of delivery, the infant was excluded.

Subjects were identified by prescreening mothers in labor and delivery by research coordinators or by notification of the research team from the neonatal or obstetrical provider. Written informed consent was obtained from the parent by an investigator before delivery. Because the neonatal team needed to be adjacent to the mother to provide resuscitation, they could not be blinded to the intervention.

At delivery, the attending team randomized (via computer-generated sequentially numbered opaque envelopes) each infant to receive 1-minute or 5-minute DCC. Infants randomized to the 1-minute group had their umbilical cord clamped and cut by 1 minute and were placed either on the mother's abdomen or, if depressed the cord was cut immediately (within seconds), they were transitioned to the radiant warmer. Resuscitation was defined as receiving stimulation to breathe, blow by oxygen,

BP	Blood pressure
DCC	Delayed cord clamping
FTOE	Fractional cerebral tissue oxygen extraction
HR	Heart rate
NICU	Neonatal intensive care unit
SpO ₂	Peripheral arterial oxygen saturation
StO ₂	Cerebral tissue oxygen saturation

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or positive pressure ventilation by endotracheal tube or mask. After the cord was cut, a pulse oximeter (Radical-7; Masimo Corporation, Irvine, California) was placed on a preductal site by the respiratory therapist. HR was first determined by a handheld Doppler probe (2 MHz, Sonoline B; Crucial Medical Systems, Shenzhen, China) and then by the pulse oximeter, which also displayed the peripheral oxygenation (SpO₂). A member of the research team attending the delivery called out both values. Data were downloaded from the pulse oximeter following delivery. Clamping time was determined by the Apgar timer and recorded.

Infants randomized to the 5-minute group were placed on the mother's abdomen if vigorous. Otherwise, they were placed on the LifeStart bed, which was equipped with resuscitation tools (Figure 2; available at www.jpeds.com) (oxygen/air blender, Neopuff Infant T-Piece Resuscitator [Fisher & Paykel Healthcare, Auckland New Zealand], portable suction). Resuscitation interventions (warm dry and stimulate initially if apneic, oxygen and/or ventilation if needed based on spontaneous breathing, SpO₂, or HR) were equivalent to the 1-minute group. If the infant did not have adequate breathing (continued need for ventilation or oxygen), clamping was delayed past the 5-minute cutoff until the infant transitioned (stable HR and SpO₂), the cord stopped pulsating, or the placenta was delivered. The research team documented all resuscitation measures at the time of the intervention.

Demographics and follow-up data were collected from all infants either in the neonatal intensive care unit (NICU) or the postpartum floor at 12 hours of life by the research team, who were blinded to the infants' group assignment. This included the primary endpoint, the StO₂, which was obtained via near-infrared spectroscopy (Foresite Monitor; Casmed, Branford, Connecticut) from a sensor placed on the forehead. The fractional cerebral tissue oxygen extraction (FTOE) was calculated (SpO₂ - StO₂/SpO₂) and recorded. Noninvasive blood pressure (BP) (Dash 3000; General Electric, Fairfield, Connecticut), HR, SpO₂, and a noninvasive hemoglobin from the oximeter acquired with the Rainbow R1-20L adhesive sensor (Masimo Corporation) also were collected at 12 hours of life.

A previous study of early and late cord clamping in infants born preterm demonstrated a 3% difference in StO₂ at 24 hours of age (68 and 71, respectively).¹⁰ Based on these previous data, at least 13 infants in each group would be required to achieve a power of 95% and an alpha of 0.05. Given that only a percentage of infants in the trial were expected to require extensive resuscitation, a larger sample of 60 subjects (n = 30 in each arm) was chosen.

We performed statistical analyses using PASW Statistics 22.0 (SPSS Inc, Chicago, Illinois). Normally distributed continuous outcome variables were compared with the unpaired Student *t* test, and nonparametric continuous outcome variables were analyzed with the Mann-Whitney *U* test. For repeated measurements tests, R (R Foundation for Statistical Computing, Vienna, Austria) and lme4 (linear mixed-effects models using Eigen and S4) were used to perform linear mixed-effects regression (lmer) analysis of the relationship between the respective treatments. Two-sided *P* < .05 was considered significant.

Table I. Demographics

Demographics	1-Minute DCC group (n = 30)	5-Minute DCC group (n = 30)	<i>P</i> value
Gestational age, wk, mean ± SD	39 ± 1.0	39 ± 1.0	.41
Birth weight, g, mean ± SD	3399 ± 510	3440 ± 523	.39
Male, n (%)	16 (53)	17 (56)	.99
Nonreassuring fetal HR, n (%)	14 (47)	13 (43)	.99
Meconium-stained amniotic fluid, n (%)	19 (63)	19 (63)	.99
Instrumentation needed for delivery, n (%)	6 (20)	2 (7)	.25
Time to cord clamping, s, mean ± SD	69 ± 35	348 ± 115	<.001
Cord pulsating when clamped, n (%)	27 (90)	6 (20)	<.001
Time to first breath/cry, s, mean ± SD	36 ± 61	25 ± 42	.43
Breathing before cord clamping, n (%)	25 (83)	30 (100)	.05
1-Minute Apgar, median (Q1, Q3)	8 (8, 8)	8 (9, 9)	.39
5-Minute Apgar, median (Q1, Q3)	8 (8, 8)	9 (9, 9)	.16

Q, quartile.

Results

Sixty infants were randomized (n = 30 per group) from August 2016 to September 2016. The mean times for DCC in the 1-minute and 5-minute groups were 1 minute, 9 seconds and 5 minutes, 48 seconds, respectively (*P* < .001, Table I). The rates of resuscitation for 1- and 5-minute groups were 63 (19/30) and 43 (13/30) (*P* = .20, Figure 3). There were 8 infants who required admission to the NICU (6 in the 1-minute and 2 in the 5-minute group, *P* = .25) for poor transition and/or tachypnea. No infants were diagnosed with hypoxic ischemic encephalopathy or required therapeutic hypothermia. Two infants (1-minute group) required oxygen at the 12-hour endpoint. One required 26% oxygen, 2-liter high flow nasal cannula. The second infant developed severe persistent pulmonary hypertension and was transferred at 24 hours of life. There were no differences between groups in HR (Figure 3) or SpO₂ (Figure 3) for the first 5 minutes in the overall group, but infants undergoing 5-minute DCC who did not receive supplemental oxygen or positive pressure ventilation had greater SpO₂ levels at 3 and 4 minutes of life (*P* = .03, Figure 3). There were no differences in postnatal noninvasive hemoglobin, bilirubin, SpO₂, or HR at 12 hours of life. Infants in the 5-minute group had greater mean BP (53 ± 13 vs 47 ± 7, *P* = .02), StO₂ (82 ± 5 vs 79 ± 7, *P* = .02), and decreased FTOE (0.15 ± .05 vs 0.18 ± .06, *P* = .03, Table II) compared with the 1-minute cord-clamping group.

Discussion

This randomized clinical trial evaluated 1 vs 5 minutes of DCC in newborns born at term at risk for resuscitation. We demonstrated that 5-minute DCC could be accomplished safely without compromising the ability to perform resuscitation and was associated with increased StO₂, decreased FTOE, and greater BP at 12 hours of life. Immediate improvements in postnatal transition, such as greater SpO₂, were identified in newborns not requiring supplemental oxygen or positive pressure

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