Delayed Cord Clamping in Infants with Suspected Intrauterine Growth Restriction

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We evaluated a subset of infants with suspected intrauterine growth restriction or birth weights small for gestational age enrolled in a study of delayed cord clamping for preterm infants. Compared with immediate clamping, delayed cord clamping was associated with no apparent harm and less suspected necrotizing enterocolitis. *(J Pediatr 2018;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT00818220 and NCT01426698.

We report a secondary analysis of a subset of infants with suspected intrauterine growth restriction (IUGR) or birth weight (BW) small for gestational age (SGA) enrolled in a larger clinical trial of delayed cord clamping (DCC) for preterm infants.[1] IUGR occurs when a fetal weight is <10th percentile for gestational age as determined with ultrasound examination.[2] Infants with IUGR are at increased risks of perinatal morbidity and mortality[2-5] as well as chronic diseases in early childhood and later life.[6,7] Previous cord clamping studies have excluded neonates with suspected IUGR before birth or not reported their outcomes separately; therefore, the effect of DCC in these infants remains unknown. Current evidence suggests that IUGR is a result of placental changes owing to a lack of adequate resources to support fetal growth (such as maternal undernutrition and failure to increase uteroplacental blood flow) creating outcomes for these infants that differ from expectations of normal infants.[8]

Previously in the main trial, we reported that DCC improved motor function by reducing the incidence of motor composite scores <85 at 18-22 months of corrected age.[1] The recent meta-analysis by Fogarty et al of 2834 preterm infants exposed to immediate cord clamping (ICC) or DCC reported that there was a significant increase in mortality (30%) in the ICC group as well as an increased risk of neonatal red blood cell transfusion and lower hematocrit levels at 4 hours of age,[9] but they did not analyze infants with growth restriction separately.

The decision to enroll a preterm infant in a trial of DCC or to provide DCC must be made prenatally before one can confirm the infant's weight. Thus, we included infants with either suspected fetal IUGR or BWs that were SGA in this secondary analysis to produce a representative sample.

BW	Birth weight
DCC	Delayed cord clamping
ICC	Immediate cord clamping
IUGR	Intrauterine growth restriction
NEC	Necrotizing enterocolitis
PROM	Premature rupture of membranes
PTL	Preterm labor
PW	Placental weight
SGA	Small for gestational age

Methods

Methods for the primary study have been described in the report of the main trial.[1] Briefly, this cohort was a subgroup of preterm infants enrolled in the DCC trial conducted at Women and Infants' Hospital of Rhode Island from February 2008 to March 2014. The trial was registered at clinicaltrials.gov (NCT00818220 and NCT01426698). Women with a singleton pregnancy estimated at $24^{0/7}$-$31^{6/7}$ weeks of gestation by obstetrical evaluation were eligible irrespective of mode of delivery. Exclusion criteria included multiple gestation, prenatally diagnosed major congenital anomalies, severe or multiple maternal illnesses, and mothers who were at risk for loss to follow-up. All the infants with suspected IUGR before birth or SGA at birth in the trial were included in this subgroup analysis.

For the DCC group, the infant was held 10-15 inches below the introitus at vaginal delivery, or below the level of placenta at cesarean delivery. At 30-45 seconds after birth, the obstetrician milked the cord once, then clamped and cut the cord. If unable to complete the protocol as planned, the obstetrician was to milk the cord quickly 2-3 times before clamping. Clamping the cord before 30 seconds after delivery with no cord milking was considered as a protocol violation. For the ICC group, the cord was routinely clamped and cut within 10 seconds after delivery as was standard at the time. Both groups received usual care by the neonatal team after cord clamping.

Primary outcomes were intraventricular hemorrhage and late-onset sepsis. Secondary outcomes included safety variables (Apgar scores at 1 and 5 minutes, body temperature at neonatal intensive care unit admission, peak serum bilirubin

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The main study was funded by the National Institute of Nursing Research (RO1 NR100015), and the 18-month follow-up was funded by the Thrasher Research Fund (9185). J.P. serves as an Editorial Board member for *The Journal of Pediatrics*. The authors declare no conflicts of interest.

Portions of this study were presented at the Pediatric Academic Societies annual meeting, May 6-9, 2017, San Francisco, California, and at the 2nd Congress of Joint European Neonatal Societies, October 31-November 4, 2017, Venice, Italy.

https://doi.org10.1016/j.jpeds.2018.05.028

in the first week, initial mean blood pressure, and initial hematocrit), bronchopulmonary dysplasia, suspected or confirmed necrotizing enterocolitis (NEC), and motor development at 18 months of corrected age. Intraventricular hemorrhage was defined as bleeding in the brain assessed by cranial ultrasound readings using Papile criteria.[10] Suspected NEC was defined as feeding intolerance with a 24-hour nothing-by-mouth order and an order for abdominal radiograph. Confirmed NEC was defined as at least a stage II in the modified Bell staging criteria.[11,12] The Bayley Scales of Infant and Toddler Development, Third Edition, was used to assess motor functions at 18-22 months of corrected age.[13] In our cohort, the diagnoses of preterm labor (PTL) and premature rupture of membranes (PROM) were not discrete among the subjects. Consequently, we combined them into 1 variable (PROM/PTL) that represented women who had either diagnosis because both conditions may be associated with intrauterine inflammation.[14]

We examined mothers' admission and hospital course notes to determine suspected IUGR and absent end-diastolic flow or reversed end-diastolic flow of the umbilical artery on Doppler imaging. Infants with SGA were identified from neonatal intensive care unit admission notes using fetal growth percentiles developed by Richardson, Alexander, and Fenton.[15-17] Placental pathology reports were evaluated to identify infants with placental weights (PW) <10th percentile for gestational age. Those who had placentas <10th percentile but were not diagnosed with suspected IUGR or SGA were reported separately.

Statistical tests included 2-sample *t* tests for continuous variables with normal distributions, Wilcoxon rank sum tests for continuous variables with non-normal distributions, and Pearson χ^2 tests and Fisher exact tests for categorical variables. A sensitivity analysis was conducted among infants with only the SGA diagnosis at birth. No adjustments were used to correct for multiple comparisons, because the endpoints being tested were largely uncorrelated, and universal adjustments would increase the likelihood of a type II error.[18] All analyses were conducted according to intention to treat. Differences between groups were considered significant when the *P* value was <.05. All analyses were performed in SAS Studio 3.5 (SAS Institute Inc, Cary, North Carolina).

Results

Fifty-seven infants from our main cohort of 211 preterm infants had a diagnosis of suspected IUGR before birth (n = 51) or a diagnosis of SGA after birth (n = 39). Eleven infants (19%) were delivered primarily because of IUGR. Seventeen were noted to have absent end-diastolic flow and 4 of the 17 also had reversed end-diastolic flow on umbilical artery Doppler assessment. Because these represent cases with the most severe IUGR, we looked at them separately despite the small numbers.

There were no differences between infants with IUGR/SGA receiving DCC or ICC at birth on maternal, infant, and perinatal characteristics except that more infants in the DCC group had mothers with PROM/PTL than those in the ICC group (**Table I**). There were no sex differences between the groups. Pre-eclampsia was significantly more common in the suspected IUGR/SGA group than in the whole study cohort as expected (61% vs 17%; $P < .0001$). Per protocol, suspected IUGR infants in the DCC group had longer cord clamping times and were more likely to receive cord milking.

PW and BW:PW stratified by gestational age are reported in **Table I**. Among the mothers of the preterm infants without

Table I. Maternal, fetal, and perinatal characteristics

	IUGR		Non-IUGR	
Variables	**DCC (n = 25)**	**ICC (n = 32)**	**DCC (n = 78)**	**ICC (n = 73)**
Maternal age (y)	30 ± 7	31 ± 6	28 ± 7	28 ± 6
Race, white	13 (52)	24 (75)	43 (56)	45 (62)
Gestational age (wk)	29 ± 2	29 ± 2	28 ± 2	28 ± 2
24-27$^{6/7}$/28-31$^{6/7}$	4/21	9/23	31/47	27/46
Main reason for preterm birth				
IUGR	4 (16)	7 (22)	—	—
Pre-eclampsia	14 (56)	21 (66)	8 (10)	17 (23)
PROM/PTL	7 (28)*	2 (6)	70 (90)*	55 (75)
Suspected IUGR in fetus	21 (84)	30 (94)	—	—
AEDF on Doppler	5 (20)	12 (38)	—	—
Cord clamping time (s)	35 (3-51)*	4 (2-18)	39 (0-60)*	5 (0-45)
Cord milked	20 (80)*	2 (6)	54 (69)*	6 (8)
BW (g)	1020 ± 303	940 ± 261	1263 ± 349	1223 ± 351
Neonatal SGA, <3%/<10%	4/10	9/16	—	—
PW (g)†	182 ± 51	160 ± 46	250 ± 75	242 ± 80
Placental SGA (<10%)	23 (92)	27 (87)	23 (30)	25 (35)
BW:PW‡	5.6 ± 1.0	6.0 ± 1.4	5.2 ± 1.0	5.3 ± 1.2
24-27$^{6/7}$	5.1 ± 1.1	5.4 ± 1.1	4.9 ± 1.1	5.0 ± 1.3
28-31$^{6/7}$	5.8 ± 1.0	6.3 ± 1.5	5.3 ± 0.9	5.5 ± 1.1

AEDF, Absent end-diastolic flow.
Mean ± SD, n (%), or median (full range).
*$P < .05$.
†Placenta reports were missing for 1 infant with suspected IUGR and 2 infants without suspected IUGR.
‡BW:PW; placentas were weighed after trimming, that is, removal of umbilical cord and membranes.

CRP 5.5.0 DTD ■ YMPD10013_proof ■ June 25, 2018