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Early Cardiac and Cerebral Hemodynamics with Umbilical Cord Milking Compared with Delayed Cord Clamping in Infants Born Preterm

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Abstract

Objective: To evaluate changes in cerebral oxygenation, peripheral arterial oxygenation, respiratory status and administered fraction of inspired oxygen (FiO_2)during the first 10 minutes of life in premature infants receiving umbilical cord milking compared with delayed cord clamping .

Study design: Premature infants born at $23^{0/7}$ to $27^{6/7}$ weeks of gestation were randomized to UCM or DCC. A near infrared spectroscopy sensor, pulse oximeter and electrocardiogram electrodes were placed. Pulse rate, cerebral tissue oxygenation (StO_2), peripheral oxygen saturation (SpO_2), airway pressure, and FiO_2 were collected for 10 minutes in the delivery room. Longitudinal models were used to compare effects of UCM and DCC.

Results: Fifty-six infants had cerebral oximetry and advanced monitoring at birth. There was an increased incidence of severe intraventricular hemorrhage in infants who received UCM compared with DCC ($p = 0.0211$). Longitudinal models suggested that SpO_2 was higher in the UCM group in the first 4 minutes ($p=0.0221$); and mean airway pressures were lower in the UCM group after the first 7 minutes ($p=0.0072$). No statistical differences were observed for FiO_2, StO_2, or heart rates.

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Conclusions: The data suggest that the rapid transfer of blood during UCM may facilitate lung expansion with improved pulmonary blood flow but may also increase cerebral blood flow resulting in severe intraventricular hemorrhage.

Trial Registration: ClinicalTrials.gov: NCT03145142

The current practice for all newborn infants is to delay the clamping and cutting of the umbilical cord. This practice is supported by randomized controlled trials and meta-analyses, and it is endorsed by several governing bodies. [1–3] However, its implementation, particularly in the extremely preterm infant, remains challenging.[1, 3] This is mostly due to the perceived need for immediate resuscitation due to poor respiratory effort and fear for hypoxia and bradycardia due to delaying resuscitation. During intact umbilical cord milking (UCM), the umbilical cord is squeezed towards the infant several times before clamping. UCM may have advantages over waiting to initiate resuscitation with delayed cord clamping (DCC). However, we demonstrated that UCM increased the risk of severe intraventricular hemorrhage (IVH) compared with DCC of 60 seconds in infants born at $23^{0/7}$ −$27^{6/7}$ weeks of gestation (PREMOD2: PREmature infants receiving Milking Or Delayed cord clamping at birth; registered at ClinicalTrials.gov: NCT03145142).[4]

As part of the PREMOD2 trial we conducted a sub-study that included additional hemodynamic investigations involving advanced delivery room monitoring and collection of delivery room data. Data pertaining to the influence of placental transfusion on cerebral oxygenation in the extremely preterm infant is limited. Previous observational data have shown an association between low cerebral oxygenation values and adverse outcome as determined by severity of IVH. [5,6] We sought to evaluate the changes in cerebral tissue oxygenation (StO_2), peripheral arterial oxygenation (SpO_2) measured by oximetry, ventilation or airway pressure (centimeters H_2O) with in-line monitoring, heart rates, and fraction of inspired oxygen (FiO_2) during the first 10 minutes of life in infants randomized to either DCC or UCM. We hypothesized that infants receiving UCM would have an increase in cerebral oximetry in the first 10 minutes of life.

Methods:

The entire protocol for the trial was published previously. [4] Immediately prior to delivery, the research staff or neonatal delivery team opened a sequentially numbered opaque randomization envelope from the appropriate gestational age strata ($23^{0/7}$-$27^{6/7}$ or $28^{0/7}$-$31^{6/7}$ weeks). Randomization was computer generated by the central Data Coordinating Center at University of Alabama at Birmingham based on randomly permuted blocks (sizes 2 and 4) and was additionally stratified by site. Enrollment took place between 6/2017-9/2018. The final date of follow-up was 12/2018. Infants were considered to be randomized at the time the envelope was opened. For DCC at cesarean delivery, the delivering obstetrician held the infant below the level of the incision for at least 60 seconds in warm, sterile towels. Infants were dried and given gentle tactile stimulation to promote respiratory effort. For vaginal delivery, the obstetrician held the infant below the level of the introitus for at least 60 seconds in warm sterile towels and provided gentle stimulation. For UCM, the obstetrician held the infant below the level of the cesarean incision (or below the level of the introitus for vaginal delivery) and 20 cm of the umbilical cord was milked for

approximately 2 seconds allowing refill, and then repeated 3 times. In an effort to ensure consistency, participating sites video recorded each technique and reviewed it with the lead principal investigator prior to enrollment of the first participant.

Patient StO_2 using near infrared spectroscopy (NIRS) for the first ten minutes after birth was collected in 4 Level III neonatal intensive care units located in the USA, Ireland, Germany, and Canada. The inclusion criteria for enrollment in this sub-study were: 1) gestational age (GA): $23^{0/7}$-$27^{6/7}$ weeks, 2) Enrollment in the main PREMOD2 trial[4] and 3) NIRS data available within 10 minutes after birth. Once the infant was randomized to the intervention (1:1 UCM or DCC), a NIRS sensor (Foresight Elite, CAS Medical Systems, Branford, CT) was placed on the infant's forehead and a pulse oximeter placed on the right palm or wrist (pre-ductal). Pulse rate, StO_2, SpO_2, airway pressure, and FiO_2 were collected for 10 minutes in the delivery room. Although arterial saturation and heart rate data were available to the clinical team, data from NIRS was blinded to practitioners. Measurements of cerebral StO_2, SpO_2 and heart rate by pulse oximetry, mean airway pressure, and FiO2 were recorded every 2 seconds. Data were captured using a purpose-built digital data acquisition system, (MP150, Biopac, Goleta CA) in the delivery room at Sharp Mary Birch Hospital in San Diego. A respiratory profile monitor (NM2, Phillips Healthcare, Electronics Ltd. Markham, ON, Canada) was used at the Royal Alexandra Hospital in Edmonton, Alberta, Canada. At University Medical Center Ulm data were collected using the NewLifeBox Neo-RSD system (Advanced Life Diagnostics, Germany) in the delivery suite. At Cork University Maternity Hospital data were acquired using a universal interface module attached to a data acquisition system (Moberg Neuromonitoring System, United Kingdom). In the NICU, StO_2 data were collected using the Biopac and heart rate by electrocardiogram; whereas mean arterial pressure and SpO_2 were captured from the bedside monitor (Carescape, GE Healthcare, Milwaukee, WI). Data on all infants participating in the NIRS study were recorded for first 10 minutes in the delivery room. Heart rate, oxygen saturations, and cerebral oxygenation, were downloaded as per each site's practice for neonatal resuscitation. Data from all sites were then processed to remove artifact prior to uploading to the Data Coordinating Center.

As this was a pilot study there was no power calculation available to estimate sample size. We planned to collect data on 200 infants, however as the study was stopped early due to increased rates of severe IVH in the UCM group, we present the available data here.

Statistical Analyses:

Descriptive statistics were calculated by treatment group for maternal and neonatal baseline characteristics and for neonatal outcomes. Neonatal outcomes were formally compared using 2-sample *t*-tests for continuous variables and chi-squared tests or Fisher exact tests for categorical variables. The primary oxygenation outcomes were all measured on continuous scales. Although we originally planned to enroll 200 infants in this sub-study, the final sample size was considerably smaller following the early stopping decision.[4] Using a two sample t-test assuming equal variance, our available sample size of 27 infants with UCM and 29 infants with DCC provided at least 80% power to detect a difference of 0.75 standard deviations for all oxygenation outcomes. Longitudinal models fit by generalized estimating equations (GEE) [7] were used to assess differences between UCM and DCC for NIRS

measures in the first 10 minutes after birth. All GEE models included the following covariates: gestational age, mode of delivery (cesarean vs vaginal), infant sex, maternal chorioamnionitis, antenatal steroids, and occurrence of severe IVH. Adjusted mean differences and 95% confidence intervals (CI) from the GEE models were calculated for the treatment group effect for minutes 1-10. Variability estimators were based on robust standard errors. An auto-regressive order-one covariance structure was used in all GEE models. Statistical hypothesis tests were evaluated at a 0.05 alpha level and no adjustments for multiple testing were performed. SAS 9.4 was used for all analyses.

Results:

Fifty-six infants had cerebral oximetry and other additional monitoring at birth (Figure 1; available at www.jpeds.com). The demographics and neonatal outcomes are shown in Table 1 and Table 2, respectively. There were no differences in baseline maternal or neonatal characteristics. There was an increased incidence of severe IVH in infants with GA of $23^{0/7}$-$27^{6/7}$ weeks after UCM compared with DCC (5 [19%] vs. 0 [0%], $P = .0211$). Figure 2 displays predicted means from GEE models. GEE models suggested that SpO_2 was higher in the UCM group in the first 4 minutes (p=0.0221); and mean airway pressures (inclusive of continuous positive airway pressure and positive pressure ventilation) were lower in the UCM group after the first 7 minutes (p=0.0072). No statistical differences were observed between UCM and DCC for FiO_2, StO_2, or pulse rates.

There were no differences in the number of infants with a 5 minute SpO_2 <80% in the UCM and DCC groups. Mean group differences estimated by GEE models at each minute are provided in Table 3.

The GEE model for SpO_2 also showed that severe IVH was associated with lower SpO_2 on average (p = 0.0131), with a predicted mean difference (95% CI) of −23.88 (−42.73, −5.02) controlling for treatment group and other covariates. Borderline evidence was also provided for a higher SpO_2 associated with use of antenatal steroids (p = 0.0835), with a predicted mean difference (95% CI) of 13.28 (−1.76, 28.31).

In the GEE model for SpO_2, a trend was observed that infants with a severe IVH had lower SpO_2 on average compared with those without a severe IVH (p = 0.0509), with a predicted mean difference (95% CI) of −17.30 (−34.66, 0.07).

The GEE model for StO_2 provided evidence that receipt of antenatal steroids was associated with higher StO_2 on average (p < 0.0001), with a predicted mean difference (95% CI) of 24.22 (16.37, 32.07) controlling for treatment group and other covariates. The GEE model for FiO_2 showed that the occurrence of severe IVH trended toward an association with higher FiO_2 on average (p = 0.0831), with a predicted mean difference (95% CI) of 13.05 (−1.71, 27.80).

In the GEE model for FiO_2, maternal chorioamnionitis was associated with higher FiO_2 on average (p = 0.0318), with a predicted mean difference (95% CI) of 7.66 (0.67, 14.66). This same model also showed that the occurrence of severe IVH was associated with higher FiO_2 on average (p = 0.0090), with a predicted mean difference (95% CI) of 14.71 (3.67, 25.76).

The GEE model for positive airway pressure demonstrated that the occurrence of severe IVH was associated with a higher positive airway pressure on average ($p = 0.0293$), with a predicted mean difference (95% CI) of 2.41 (0.24, 4.57.

In the GEE model, antenatal steroids were associated with a lower positive airway pressure on average ($p = 0.0002$), with a predicted mean difference (95% CI) of −4.82 (−7.33, −2.32). In this same model, the occurrence of severe IVH was associated with lower airway pressure ($p = 0.0062$), with a mean difference (95% CI) of 2.95 (0.84, 5.06).

The GEE model for pulse rate provided evidence that receipt of antenatal steroids was associated with higher pulse rates ($p < 0.0071$), with a predicted mean difference (95% CI) of 28.62 (7.77, 49.46) controlling for treatment group and other covariates.

Discussion:

In this study, UCM was associated with increases in arterial oxygen saturation and decreases in mean airway pressure compared with DCC in extremely preterm infants. In other studies, both UCM and DCC were associated with improvements in heart rate, blood pressure, and systemic blood flow compared with early cord clamping in premature infants.[8–10] There are data on uncomplicated vaginal birth in more mature infants with DCC suggesting higher SpO_2 and lower heart rates compared with early cord clamping. [11] However there is very limited oximetry data comparing UCM and DCC in extremely preterm infants. Our findings suggest that there may be differences between UCM and DCC in this population immediately after birth. Higher peripheral oxygen saturation with decreased ventilatory requirement after UCM suggests improvements in pulmonary arterial blood flow. This was not seen in animal studies evaluating intact UCM in premature anesthetized lambs. This may be due to differences in the ability to increase pulmonary blood flow in the absence of ventilation. The delay in administration of ventilation and oxygen therapy with DCC may also be important. Although the number of infants with a 5 minutes SpO2 < 80 percent did not differ between groups, the lower oxygen saturation values in the DCC group in in the first 7 minutes are concerning. A post hoc exploratory analysis of the TO2rpido trial found that children with a 5-minute oxygen saturation <80% were more likely to die or have neurodevelopmental impairment (OR, 1.85; 95% CI, 1.07-3.2; P = .03). [12]

A limitation of our study is the small number of infants studied. The intervention was also not blinded to the providers. It was difficult for all centers to place the NIRS probe and therefore urgent deliveries and potentially sicker infants may have been excluded. Further our findings of higher SpO_2 and lower mean airway pressure were secondary analyses and therefore our study was not powered to detect these outcomes. Last, we did not adjust our statistical analyses for multiple comparisons.

Overall, our data suggest that the rapid transfer of blood during UCM may facilitate lung expansion with improved pulmonary blood flow but also may increase cerebral blood flow resulting in severe IVH. These short term findings need to be correlated with longer term neurodevelopmental findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

DCC	Delayed Cord Clamping
GA	Gestational Age
StO_2	cerebral tissue oxygenation
IVH	intraventricular hemorrhage
NIRS	near infrared spectroscopy
SpO_2	peripheral arterial oxygenation
FiO_2	fraction of inspired oxygen
GEE	generalized estimating equations
SE	sandwich standard error

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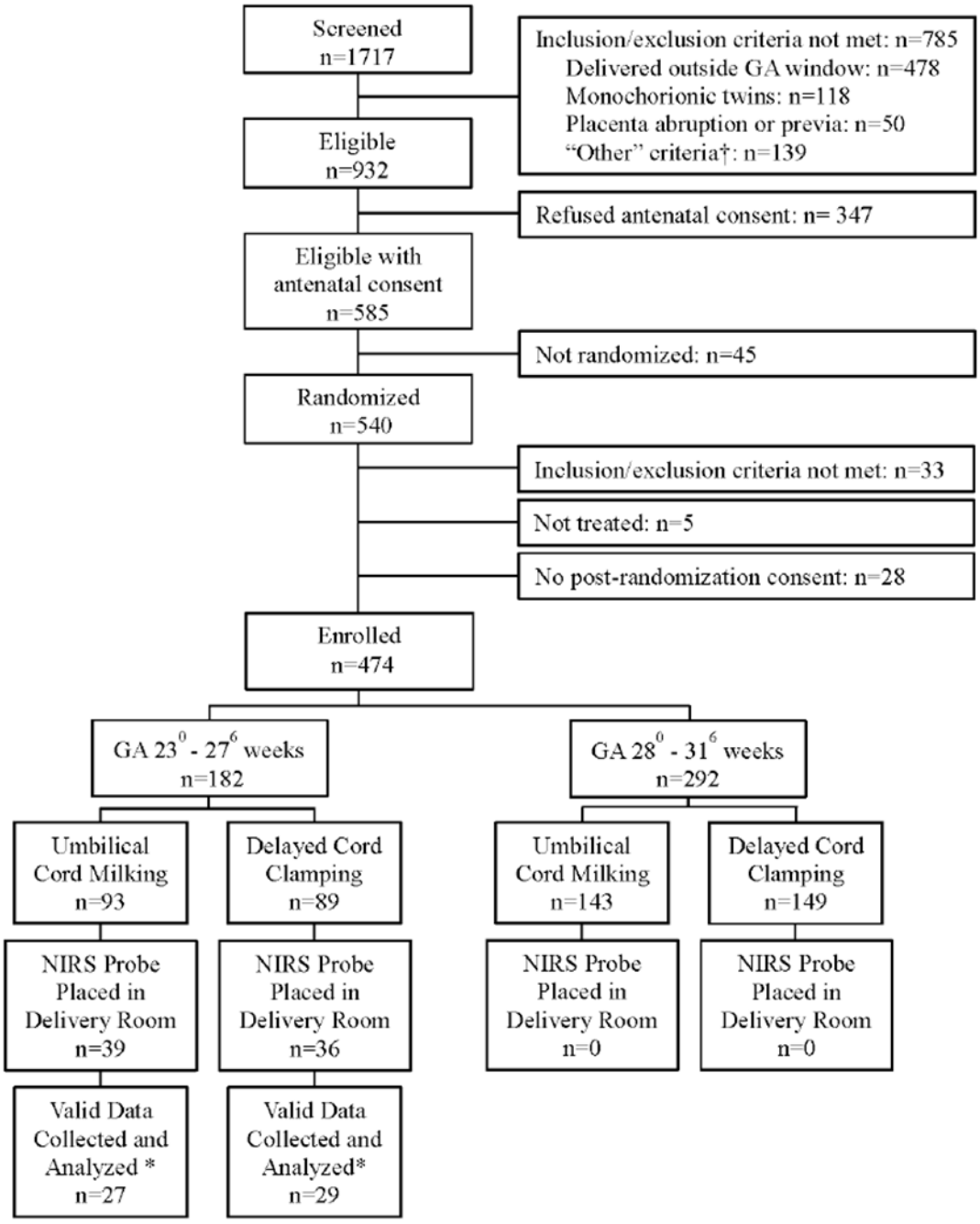

Figure 1. CONSORT flow diagram (online).

† "Other" criteria include fetal or maternal risk for severe compromise at delivery (n=30), congenital anomalies of newborn (n=27), family unlikely to return for neurodevelopmental testing at 24 months (n=22), and cardiac defects (n=11).

* The files that were not uploaded but who are indicated as having a NIRS data collected are ones for which a blank or corrupted NIRS file was collected.

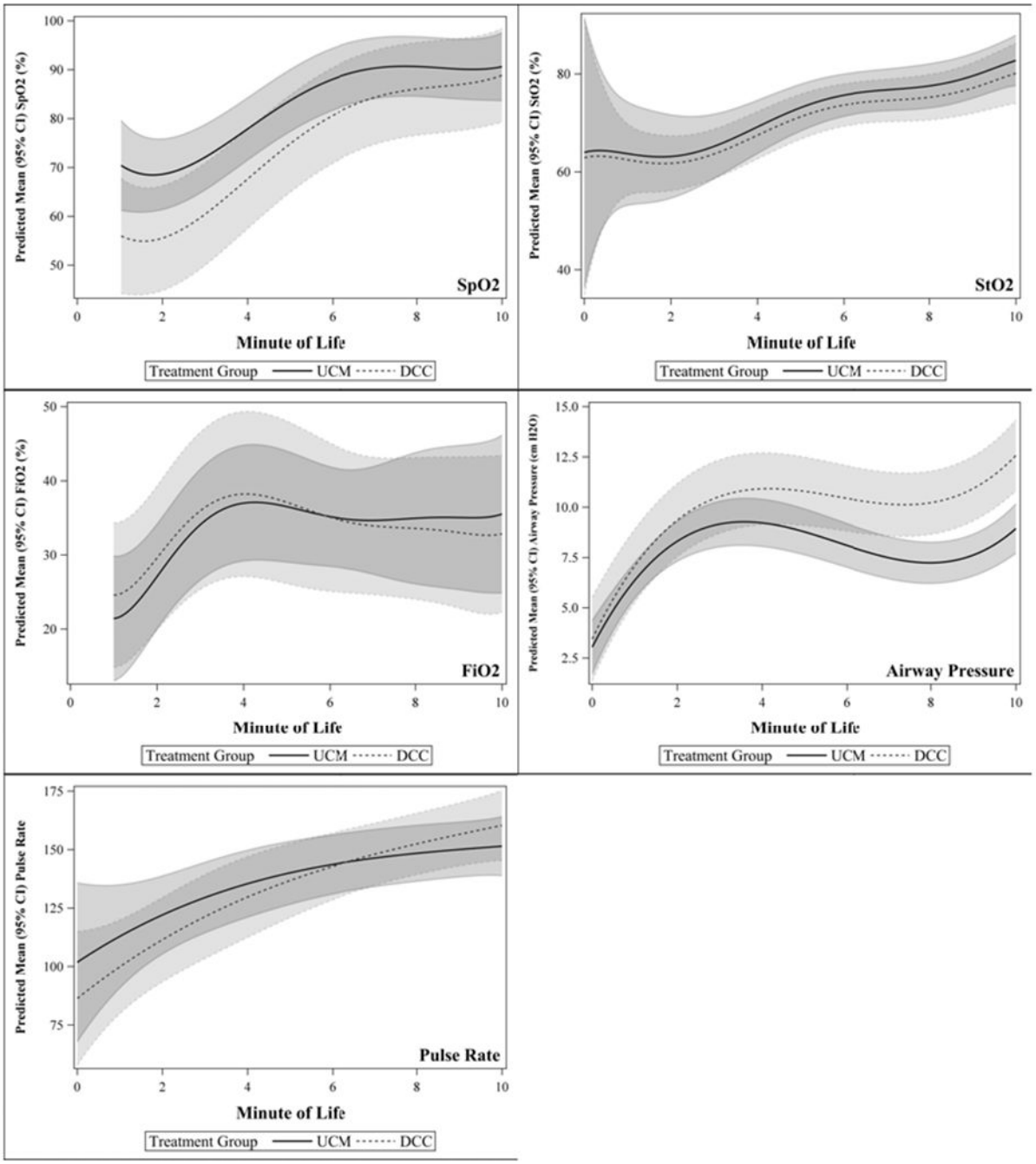

Figure 2.
Plots of predicted values of hemodynamic measures from GEE models by treatment group.

Table 1.

Baseline maternal and neonatal characteristics by Treatment Group

	Umbilical Cord Milking (N=27)	Delayed Cord Clamping (N=29)
Maternal age, years: Mean (SD)	30.8 (4.5)	30.2 (5.2)
Birth gestational age, weeks: Mean (SD)	26.2 (1.5)	25.7 (1.3)
Infant gender: N(%)		
Female	14 (52%)	19 (66%)
Male	13 (48%)	10 (34%)
Infant race: N(%)		
American Indian or Alaskan Native	2 (7%)	3 (10%)
Asian	2 (7%)	6 (21%)
Black or African American	4 (15%)	1 (3%)
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (3%)
White	15 (56%)	13 (45%)
More than One Race	3 (11%)	4 (14%)
Unknown or Not Reported	1 (4%)	1 (3%)
Infant ethnicity: N(%)		
Hispanic or Latino	11 (41%)	12 (41%)
Not Hispanic or Latino	16 (59%)	17 (59%)
Unknown or Not Reported	0 (0%)	0 (0%)
Cesarean section delivery: N(%)	23 (85%)	21 (72%)
Maternal diabetes: N(%)	1 (4%)	3 (10%)
Maternal chorioamionitis: N(%)	11 (41%)	15 (52%)
Pregnancy induced hypertension/Pre-eclampsia: N(%)	6 (22%)	4 (14%)
Labor or uterotonics before delivery: N(%)	17 (63%)	19 (66%)
Duration of rupture of membranes before delivery, hours: Median (IQR)	0 (0, 70)	0 (0, 24)
Steroids given before delivery: N(%)	25 (93%)	26 (90%)
Antenatal magnesium: N(%)	21 (78%)	21 (72%)
General anesthesia: N(%)	4 (15%)	5 (17%)
Small for gestational age: N(%)	1 (4%)	1 (3%)

Table 2.

Neonatal outcomes by treatment group

	Umbilical Cord Milking (N=27)	Delayed Cord Clamping (N=29)	*p*-value
Severe IVH or death: N(%)	6 (22%)	3 (10%)	0.2884
Severe IVH: N(%)	5 (19%)	0 (0%)	0.0211
Infant death: N(%)	4 (15%)	3 (10%)	0.7004
Any grade IVH: N(%)	9 (33%)	8 (28%)	0.6402
IVH Grades I or II: N(%)	4 (15%)	8 (28%)	0.3337
Hemoglobin at 4 (±2) hours of life (g/dL): Mean (SD)	16.0 (2.3)	15.2 (2.1)	0.1703
Hematocrit at 4 (±2) hours of life (g/dL) : Mean (SD)	48.1 (6.7)	45.0 (5.6)	0.0732
Positive pressure ventilation: N(%)	26 (96%)	26 (90%)	0.6120
Continuous positive airway pressure: N(%)	22 (81%)	18 (62%)	0.1081
Intubation: N(%)	15 (56%)	20 (69%)	0.3003
Compressions: N(%)	1 (4%)	1 (3%)	0.9999
Epinephrine: N(%)	0 (0%)	0 (0%)	0.9999
Other medications: N(%)	1 (4%)	1 (3%)	0.9999
Polycythemia in first 7 days of life: N(%)	0 (0%)	0 (0%)	0.9999
Early onset sepsis, ≤72 hours of life: N(%)	0 (0%)	1 (3%)	0.9997
Late onset sepsis, >72 hours of life: N(%)	5 (19%)	4 (14%)	0.7249
Any sepsis: N(%)	5 (19%)	5 (17%)	0.9008
Patent ductus arteriosus: N(%)	10 (37%)	15 (52%)	0.2693
Retinopathy of prematurity requiring treatment: N(%)	3 (11%)	8 (28%)	0.1808
Exchange transfusion for hyperbilirubinemia: N(%)	0 (0%)	0 (0%)	0.9999
Chronic lung disease: N(%)	8 (30%)	11 (38%)	0.5121
Necrotizing enterocolitis: N(%)	1 (4%)	2 (7%)	0.9997
Spontaneous intestinal perforation: N(%)	0 (0%)	0 (0%)	0.9999
Periventricular leukomalacia: N(%)	6 (22%)	0 (0%)	0.0091

Table 3.

Predicted treatment group effects on hemodynamic measures over time from GEE models.

	Minute of Life	Mean Difference Estimate (95% CI)[†]	*p*-value
SpO_2 (%)[‡]	1	14.30 (2.40, 26.19)	0.0185 *
	2	13.16 (2.34, 23.98)	0.0171 *
	3	12.03 (2.19, 21.87)	0.0165 *
	4	10.90 (1.91, 19.88)	0.0174 *
	5	9.77 (1.47, 18.06)	0.0210 *
	6	8.64 (0.82, 16.45)	0.0304 *
	7	7.50 (−0.09, 15.10)	0.0527
	8	6.37 (−1.27, 14.01)	0.1020
	9	5.24 (−2.71, 13.19)	0.1965
	10	4.11 (−4.40, 12.61)	0.3437
StO_2 (%)	1	−0.31 (−9.77, 9.14)	0.9480
	2	0.37 (−7.97, 8.70)	0.9315
	3	1.05 (−6.26, 8.35)	0.7791
	4	1.73 (−4.67, 8.12)	0.5971
	5	2.41 (−3.27, 8.08)	0.4063
	6	3.09 (−2.14, 8.31)	0.2467
	7	3.77 (−1.34, 8.87)	0.1479
	8	4.45 (−0.89, 9.79)	0.1027
	9	5.13 (−0.77, 11.02)	0.0882
	10	5.81 (−0.88, 12.49)	0.0887
FiO_2 (%)[‖]	1	−1.25 (−12.18, 9.68)	0.8230
	2	−0.82 (−10.44, 8.79)	0.8665
	3	−0.40 (−9.05, 8.24)	0.9273
	4	0.02 (−8.11, 8.15)	0.9962
	5	0.44 (−7.71, 8.59)	0.9154
	6	0.86 (−7.85, 9.58)	0.8459
	7	1.29 (−8.43, 11.01)	0.7953
	8	1.71 (−9.34, 12.76)	0.7619
	9	2.13 (−10.47, 14.73)	0.7404
	10	2.55 (−11.75, 16.86)	0.7265
Positive airway pressure (cm H2O)[†]	1	−0.68 (−2.55, 1.19)	0.4781
	2	−1.01 (−2.71, 0.70)	0.2484
	3	−1.33 (−2.91, 0.25)	0.0980
	4	−1.66 (−3.16, −0.16)	0.0297 *
	5	−1.99 (−3.46, −0.52)	0.0080 *
	6	−2.32 (−3.81, −0.82)	0.0024 *
	7	−2.64 (−4.22, −1.07)	0.0010 *

	Minute of Life	Mean Difference Estimate (95% CI)[†]	*p*-value
	8	−2.97 (−4.68, −1.27)	0.0006 *
	9	−3.30 (−5.17, −1.43)	0.0005 *
	10	−3.63 (−5.69, −1.57)	0.0006 *
Pulse rate (bpm)	1	20.62 (−1.47, 42.70)	0.0673
	2	18.32 (−1.77, 38.41)	0.0738
	3	16.03 (−2.23, 34.29)	0.0853
	4	13.74 (−2.92, 30.40)	0.1060
	5	11.45 (−3.91, 26.80)	0.1440
	6	9.15 (−5.27, 23.57)	0.2136
	7	6.86 (−7.09, 20.81)	0.3350
	8	4.57 (−9.40, 18.53)	0.5217
	9	2.27 (−12.21, 16.76)	0.7584
	10	−0.02 (−15.47, 15.43)	0.9980

[†]Mean differences here are calculated with the reference group being the delayed cord clamping group. Thus the predicted mean difference point estimates displayed here are calculated by subtracting the predicted mean for the delayed cord clamping group from the predicted mean for the umbilical cord milking group. This is done for each NIRS measure at each minute of life.

[‡]The GEE model for SpO_2 also provided some evidence that infants with a severe IVH had lower SpO_2 on average compared to those without a severe IVH ($p = 0.0509$); with a predicted mean difference (95% CI) of −17.30 (−34.66, 0.07) associated with occurrence of severe IVH.

[▪]The GEE model for FiO_2 also suggests that presence of maternal chorioamnionitis was associated with higher FiO_2 on average ($p = 0.0318$); with a predicted mean difference (95% CI) of 7.66 (0.67, 14.66) associated with presence of maternal chorioamnionitis. This same model also suggests occurrence of severe IVH was associated with higher FiO_2 on average ($p = 0.0090$); with a predicted mean difference (95% CI) of 14.71 (3.67, 25.76) associated with occurrence of severe IVH.

[▪]The GEE model for positive airway pressure also suggests that occurrence of severe IVH was associated with a higher positive airway pressure on average ($p = 0.0293$); with a predicted mean difference (95% CI) of 2.41 (0.24, 4.57) associated with occurrence of severe IVH.

*$p < 0.05$.