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

Study design Premature infants born at $23^{0/7}$ to $27^{6/7}$ weeks of gestation were randomized to umbilical cord milking or DCC. A near infrared spectroscopy sensor, pulse oximeter, and electrocardiogram electrodes were placed. Pulse rate, cerebral tissue oxygenation, peripheral oxygen saturation, airway pressure, and fraction of inspired oxygen were collected for 10 minutes in the delivery room. Longitudinal models were used to compare effects of umbilical cord milking 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 umbilical cord milking compared with DCC ($P = .0211$). Longitudinal models suggested that peripheral oxygen saturation was higher in the umbilical cord milking group in the first 4 minutes ($P = .0221$) and that mean airway pressures were lower in the umbilical cord milking group after the first 7 minutes ($P = .0072$). No statistical differences were observed for fraction of inspired oxygen, cerebral tissue oxygenation, or heart rates.

Conclusions The data suggest that the rapid transfer of blood during umbilical cord milking may facilitate lung expansion with improved pulmonary blood flow, but may also increase cerebral blood flow, resulting in severe intraventricular hemorrhage. *(J Pediatr 2020; ■:1-6)*.

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 difficulty is mostly due to the perceived need for immediate resuscitation owing to poor respiratory effort and fear for hypoxia and bradycardia owing to delaying resuscitation. During intact umbilical cord milking, the umbilical cord is squeezed toward the infant several times before clamping. Umbilical cord milking may have advantages over waiting to initiate resuscitation with delayed cord clamping (DCC). However, we demonstrated that umbilical cord milking 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 substudy 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 are 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 (cm 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 umbilical cord milking. We hypothesized that in-

DCC	Delayed cord clamping
FiO_2	Fraction of inspired oxygen
GEE	Generalized estimating equations
IVH	Intraventricular hemorrhage
StO_2	Cerebral tissue oxygenation
NIRS	Near infrared spectroscopy
PREMOD2	PREmature infants receiving Milking Or Delayed cord clamping at birth
SpO_2	Peripheral arterial oxygenation

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fants receiving umbilical cord milking 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 before 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 June 2017 and September 2018. The final date of follow-up was December 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 umbilical cord milking, 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 before enrollment of the first participant.

Patient StO_2 using near infrared spectroscopy (NIRS) for the first 10 minutes after birth was collected in 4 level III neonatal intensive care units located in the US, Ireland, Germany, and Canada. The inclusion criteria for enrollment in this substudy were: (1) gestational age of $23^{0/7}$-$27^{6/7}$ 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 umbilical cord milking or DCC), a NIRS sensor (Foresight Elite, CAS Medical Systems, Branford, Connecticut) was placed on the infant's forehead and a pulse oximeter placed on the right palm or wrist (preductal). 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 were blinded to practitioners. Measurements of cerebral StO_2, SpO_2 and heart rate by pulse oximetry, mean airway pressure, and FiO_2 were recorded every 2 seconds. Data were captured using a purpose-built digital data acquisition system (MP150, Biopac, Goleta, California) in the delivery room at Sharp Mary Birch Hospital in San Diego. A respiratory profile monitor (NM2, Phillips Healthcare, Electronics Ltd, Markham, Ontario, Canada) was used at the Royal Alexandra Hospital in Edmonton, Alberta, Canada. At the University Medical Center Ulm, data were collected using the NewLife-Box Neo-RSD system (Advanced Life Diagnostics, Weener, 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, Ambler, Pennsylvania). In the neonatal intensive care unit, StO_2 data were collected using the Biopac and heart rate by electrocardiogram, and the mean arterial pressure and SpO_2 were captured from the bedside monitor (Carescape, GE Healthcare, Milwaukee, Wisconsin). 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 before uploading to the Data Coordinating Center.

Because this was a pilot study, there was no power calculation available to estimate sample size. We planned to collect data on 200 infants; however, because as the study was stopped early owing to increased rates of severe IVH in the umbilical cord milking 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 χ^2 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 substudy, the final sample size was considerably smaller after the early stopping decision.[4] Using a 2-sample t test assuming equal variance, our available sample size of 27 infants with umbilical cord milking and 29 infants with DCC provided at least 80% power to detect a difference of 0.75 SDs for all oxygenation outcomes. Longitudinal models fit by generalized estimating equations (GEE)[7] were used to assess differences between umbilical cord milking 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% CIs from the GEE models were calculated for the treatment group effect for minutes 1-10. Variability estimators were based on robust standard errors. An autoregressive 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 (SAS Institute, Cary, North Carolina).

Results

Fifty-six infants had cerebral oximetry and other additional monitoring at birth (**Figure 1**; available at www.jpeds.

Table I. Baseline maternal and neonatal characteristics by treatment group

Characteristics	Umbilical cord milking (n = 27)	DCC (n = 29)
Maternal age, y	30.8 ± 4.5	30.2 ± 5.2
Birth gestational age, wk	26.2 ± 1.5	25.7 ± 1.3
Infant sex		
Female	14 (52)	19 (66)
Male	13 (48)	10 (34)
Infant race		
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 1 race	3 (11)	4 (14)
Unknown or not reported	1 (4)	1 (3)
Infant ethnicity		
Hispanic or Latino	11 (41)	12 (41)
Not Hispanic or Latino	16 (59)	17 (59)
Unknown or not reported	0 (0)	0 (0)
Cesarean delivery	23 (85)	21 (72)
Maternal diabetes	1 (4)	3 (10)
Maternal chorioamnionitis	11 (41)	15 (52)
Pregnancy-induced hypertension/preeclampsia	6 (22)	4 (14)
Labor or uterotonics before delivery	17 (63)	19 (66)
Duration of rupture of membranes before delivery, h	0 (0, 70)	0 (0, 24)
Steroids given before delivery	25 (93)	26 (90)
Antenatal magnesium	21 (78)	21 (72)
General anesthesia	4 (15)	5 (17)
Small for gestational age	1 (4)	1 (3)

Values are mean ± SD, number (%), or median (IQR).

Table II. Neonatal outcomes by treatment group

Outcomes	Umbilical cord milking (n = 27)	DCC (n = 29)	*P* value
Severe IVH or death	6 (22)	3 (10)	.2884
Severe IVH	5 (19)	0 (0)	.0211
Infant death	4 (15)	3 (10)	.7004
Any grade IVH	9 (33)	8 (28)	.6402
IVH grades I or II	4 (15)	8 (28)	.3337
Hemoglobin at 4 ± 2 h of life (g/dL)	16.0 ± 2.3	15.2 ± 2.1	.1703
Hematocrit at 4 ± 2 h of life (g/dL)	48.1 ± 6.7	45.0 ± 5.6	.0732
Positive pressure ventilation	26 (96)	26 (90)	.6120
Continuous positive airway pressure	22 (81)	18 (62)	.1081
Intubation	15 (56)	20 (69)	.3003
Compressions	1 (4)	1 (3)	.9999
Epinephrine	0 (0)	0 (0)	.9999
Other medications	1 (4)	1 (3)	.9999
Polycythemia in first 7 d of life	0 (0)	0 (0)	.9999
Early onset sepsis, ≤72 h of life	0 (0)	1 (3)	.9997
Late onset sepsis, >72 h of life	5 (19)	4 (14)	.7249
Any sepsis	5 (19)	5 (17)	.9008
Patent ductus arteriosus	10 (37)	15 (52)	.2693
Retinopathy of prematurity requiring treatment	3 (11)	8 (28)	.1808
Exchange transfusion for hyperbilirubinemia	0 (0)	0 (0)	.9999
Chronic lung disease	8 (30)	11 (38)	.5121
Necrotizing enterocolitis	1 (4)	2 (7)	.9997
Spontaneous intestinal perforation	0 (0)	0 (0)	.9999
Periventricular leukomalacia	6 (22)	0 (0)	.0091

Values are mean ± SD or number (%).

com). The demographics and neonatal outcomes are shown in **Table I** and **Table II**, respectively. There were no differences in baseline maternal or neonatal characteristics. There was an increased incidence of severe IVH in infants with a gestational age of $23^{0/7}$-$27^{6/7}$ weeks after umbilical cord milking compared with DCC (5 [19%] vs 0 [0%]; $P = .0211$). **Figure 2** displays predicted means from GEE models. GEE models suggested that the SpO_2 was higher in the umbilical cord milking group in the first 4 minutes ($P = .0221$); and mean airway pressures (inclusive of continuous positive airway pressure and positive pressure ventilation) were lower in the umbilical cord milking group after the first 7 minutes ($P = .0072$). No statistical differences were observed between umbilical cord milking 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 of less than 80% in the umbilical cord milking and DCC groups. The mean group differences estimated by GEE models at each minute are provided in **Table III**.

The GEE model for SpO_2 also showed that severe IVH was associated with lower SpO_2 on average ($P = .0131$), with a predicted mean difference (95% CI) of −23.88 (−42.73 to −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 ($P = .0835$), with a predicted mean difference of 13.28 (95% CI, −1.76 to 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 ($P = .0509$), with a predicted mean difference of −17.30 (95% CI, −34.66 to 0.07).

The GEE model for StO_2 provided evidence that receipt of antenatal steroids was associated with higher StO_2 on average ($P < .0001$), with a predicted mean difference of 24.22 (95% CI, 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 ($P = .0831$), with a predicted mean difference of 13.05 (95% CI, −1.71 to 27.80).

In the GEE model for FiO_2, maternal chorioamnionitis was associated with higher FiO_2 on average ($P = .0318$), with a predicted mean difference of 7.66 (95% CI, 0.67-14.66). This same model also showed that the occurrence of severe IVH was associated with higher FiO_2 on average ($P = .0090$), with a predicted mean difference of 14.71 (95% CI, 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 ($P = .0293$), with a predicted mean difference of 2.41 (95% CI, 0.24-4.57).

In the GEE model, antenatal steroids were associated with a lower positive airway pressure on average ($P = .0002$), with a predicted mean difference of −4.82 (95% CI, −7.33 to

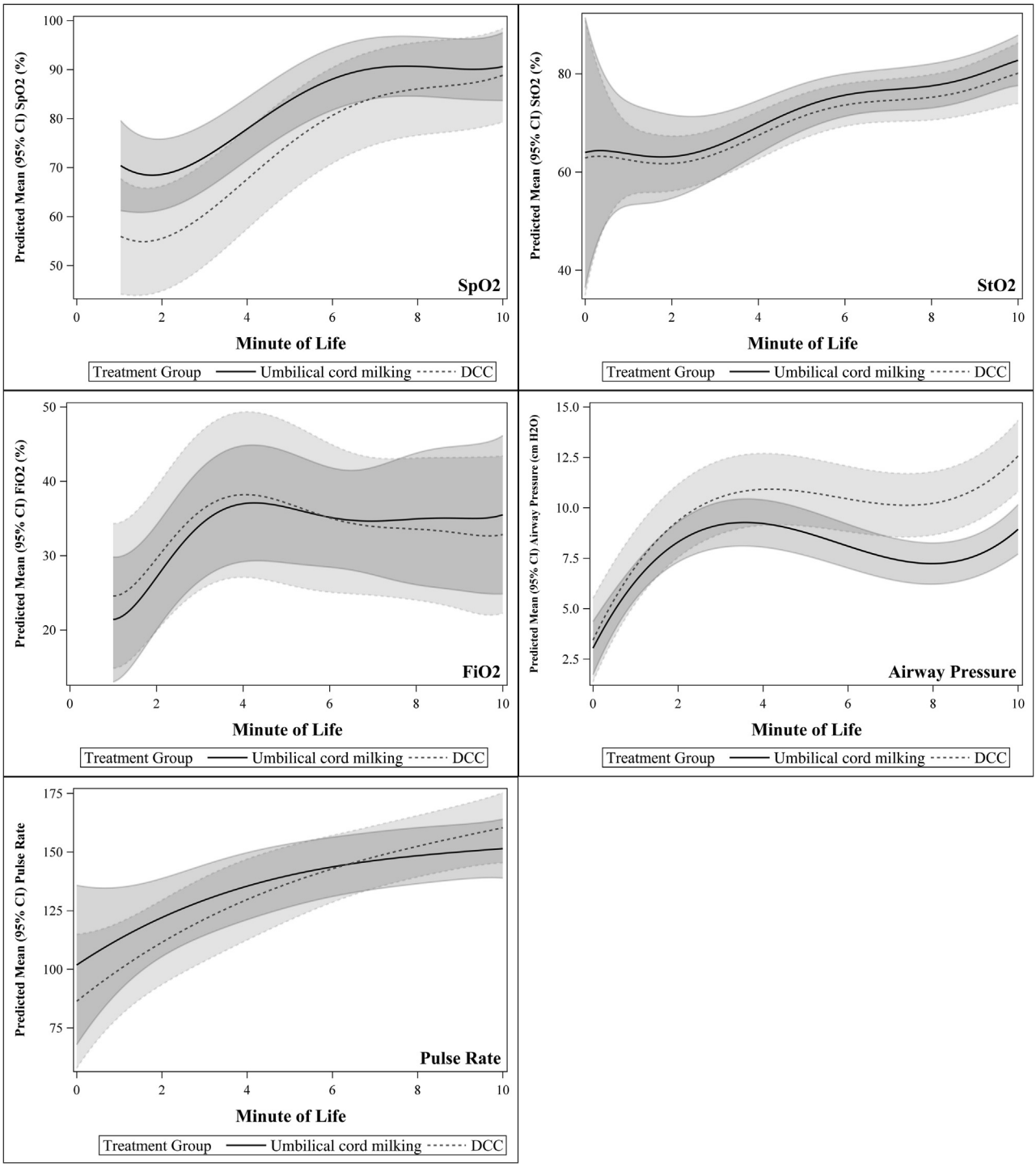

Figure 2. Plots of predicted values of hemodynamic measures from GEE models by treatment group.

−2.32). In this same model, the occurrence of severe IVH was associated with lower airway pressure (P = .0062), with a mean difference of 2.95 (95% CI, 0.84-5.06).

The GEE model for pulse rate provided evidence that receipt of antenatal steroids was associated with higher pulse rates (P < .0071), with a predicted mean difference of 28.62 (95% CI, 7.77-49.46) controlling for treatment group and other covariates.

Discussion

In this study, umbilical cord milking 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 umbilical cord milking and DCC were associated with improvements in heart rate, blood

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

Hemodynamic measures	Minute of life	Mean difference estimate (95% CI)*	*P* value
SpO_2 (%)†	1	14.30 (2.40 to 26.19)	.0185‡
	2	13.16 (2.34 to 23.98)	.0171‡
	3	12.03 (2.19 to 21.87)	.0165‡
	4	10.90 (1.91 to 19.88)	.0174‡
	5	9.77 (1.47 to 18.06)	.0210‡
	6	8.64 (0.82 to 16.45)	.0304‡
	7	7.50 (−0.09 to 15.10)	.0527
	8	6.37 (−1.27 to 14.01)	.1020
	9	5.24 (−2.71 to 13.19)	.1965
	10	4.11 (−4.40 to 12.61)	.3437
StO_2 (%)	1	−0.31 (−9.77 to 9.14)	.9480
	2	0.37 (−7.97 to 8.70)	.9315
	3	1.05 (−6.26 to 8.35)	.7791
	4	1.73 (−4.67 to 8.12)	.5971
	5	2.41 (−3.27 to 8.08)	.4063
	6	3.09 (−2.14 to 8.31)	.2467
	7	3.77 (−1.34 to 8.87)	.1479
	8	4.45 (−0.89 to 9.79)	.1027
	9	5.13 (−0.77 to 11.02)	.0882
	10	5.81 (−0.88 to 12.49)	.0887
FiO_2 (%)§	1	−1.25 (−12.18 to 9.68)	.8230
	2	−0.82 (−10.44 to 8.79)	.8665
	3	−0.40 (−9.05 to 8.24)	.9273
	4	0.02 (−8.11 to 8.15)	.9962
	5	0.44 (−7.71 to 8.59)	.9154
	6	0.86 (−7.85 to 9.58)	.8459
	7	1.29 (−8.43 to 11.01)	.7953
	8	1.71 (−9.34 to 12.76)	.7619
	9	2.13 (−10.47 to 14.73)	.7404
	10	2.55 (−11.75 to 16.86)	.7265
Positive airway pressure (cm H_20)¶	1	−0.68 (−2.55 to 1.19)	.4781
	2	−1.01 (−2.71 to 0.70)	.2484
	3	−1.33 (−2.91 to 0.25)	.0980
	4	−1.66 (−3.16 to −0.16)	.0297‡
	5	−1.99 (−3.46 to −0.52)	.0080‡
	6	−2.32 (−3.81 to −0.82)	.0024‡
	7	−2.64 (−4.22 to −1.07)	.0010‡
	8	−2.97 (−4.68 to −1.27)	.0006‡
	9	−3.30 (−5.17 to −1.43)	.0005‡
	10	−3.63 (−5.69 to −1.57)	.0006‡
Pulse rate (bpm)	1	20.62 (−1.47 to 42.70)	.0673
	2	18.32 (−1.77 to 38.41)	.0738
	3	16.03 (−2.23 to 34.29)	.0853
	4	13.74 (−2.92 to 30.40)	.1060
	5	11.45 (−3.91 to 26.80)	.1440
	6	9.15 (−5.27 to 23.57)	.2136
	7	6.86 (−7.09 to 20.81)	.3350
	8	4.57 (−9.40 to 18.53)	.5217
	9	2.27 (−12.21 to 16.76)	.7584
	10	−0.02 (−15.47 to 15.43)	.9980

*Mean differences here are calculated with the reference group being the DCC group. Thus, the predicted mean difference point estimates displayed here are calculated by subtracting the predicted mean for the DCC 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 ($P = .0509$); with a predicted mean difference of −17.30 (95% CI, −34.66 to 0.07) associated with occurrence of severe IVH.

‡$P < .05$.

§The GEE model for FiO_2 also suggests that presence of maternal chorioamnionitis was associated with higher FiO_2 on average ($P = .0318$); with a predicted mean difference of 7.66 (95% CI, 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 ($P = .0090$); with a predicted mean difference of 14.71 (95% CI, 3.67-25.76) associated with the 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 ($P = .0293$); with a predicted mean difference of 2.41 (95% CI, 0.24-4.57) associated with occurrence of severe IVH.

pressure, and systemic blood flow compared with early cord clamping in premature infants.[8-10] There are data on uncomplicated vaginal births in more mature infants with DCC suggesting higher SpO_2 and lower heart rates compared with early cord clamping.[11] However, there are very limited oximetry data comparing umbilical cord milking and DCC in extremely preterm infants. Our findings suggest that there may be differences between umbilical cord milking and DCC in this population immediately after birth. A higher peripheral oxygen saturation with decreased ventilatory requirement after umbilical cord milking suggests improvements in pulmonary arterial blood flow. This was not seen in animal studies evaluating intact umbilical cord milking 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-minute SpO_2 of 80% or less 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 of 80% or less 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; 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 umbilical cord milking 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. ■

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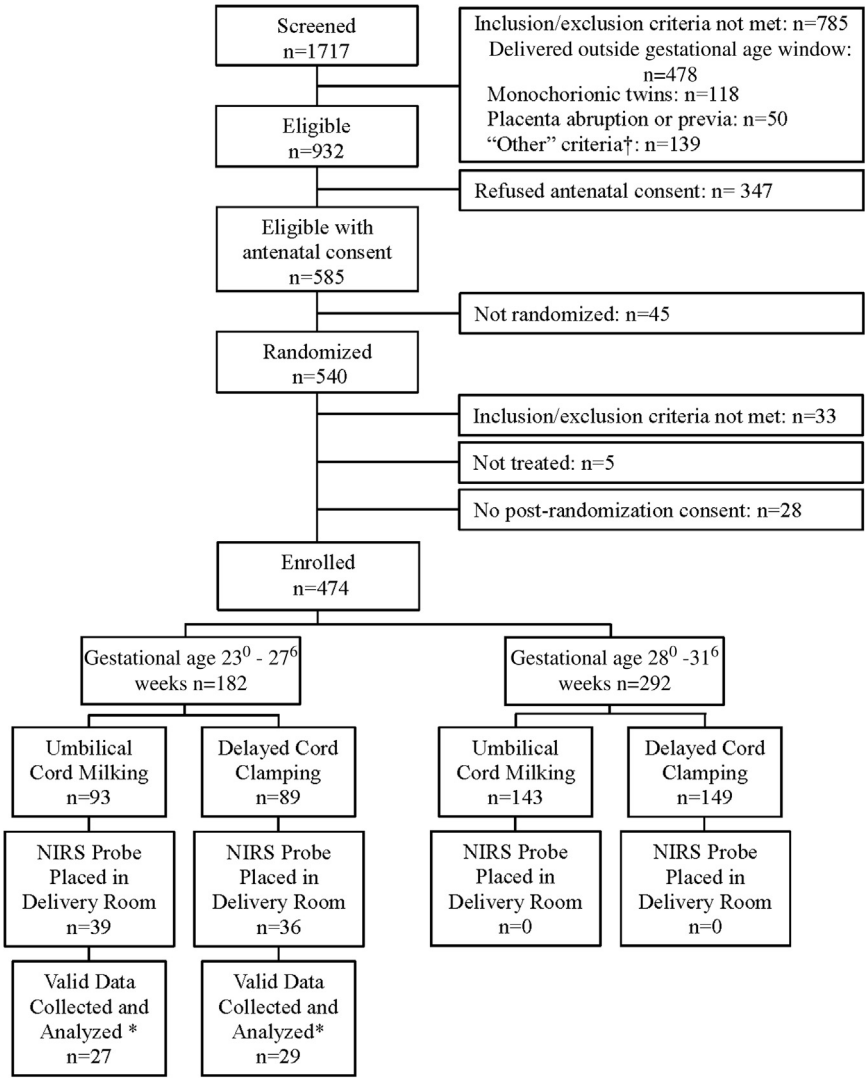

Figure 1. CONSORT flow diagram. †"Other" criteria include fetal or maternal risk for severe compromise at delivery (n = 30), congenital anomalies of newborn (n = 27), family unlikely to return for neurodevelopmental testing at 24 months (n = 22), and cardiac defects (n = 11). *The files that were not uploaded but who are indicated as having a NIRS data collected are ones for which a blank or corrupted NIRS file was collected.