Clamping the Umbilical Cord in Premature Deliveries (CUPiD): Neuromonitoring in the Immediate Newborn Period in a Randomized, Controlled Trial of Preterm Infants Born at <32 Weeks of Gestation

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Objective To compare cerebral activity and oxygenation in preterm infants (<32 weeks of gestation) randomized to different cord clamping strategies.

Study design Preterm infants born at <32 weeks of gestation were randomized to immediate cord clamping, umbilical cord milking (cord stripped 3 times), or delayed cord clamping for 60 seconds with bedside resuscitation. All infants underwent electroencephalogram (EEG) and cerebral near infrared spectroscopy for the first 72 hours after birth. Neonatal primary outcome measures were quantitative measures of the EEG (17 features) and near infrared spectroscopy over 1-hour time frames at 6 and 12 hours of life.

Results Forty-five infants were recruited during the study period. Twelve infants (27%) were randomized to immediate cord clamping, 19 (42%) to umbilical cord milking, and 14 (31%) to delayed cord clamping with bedside resuscitation. There were no significant differences between groups for measures of EEG activity or cerebral near infrared spectroscopy. Three of the 45 infants (6.7%) were diagnosed with severe IVH (2 in the immediate cord clamping group, 1 in the umbilical cord milking group; $P = .35$).

Conclusions There were no differences in cerebral EEG activity and cerebral oxygenation values between cord management strategies at 6 and 12 hours. *(J Pediatr 2019; ■:1-6)*.

Trial registration ISRCTN92719670.

Umbilical cord management allowing for placental transfusion of blood is an important intervention for preterm infant health. In some studies of preterm infants, delayed cord clamping or umbilical cord milking have been shown to decrease the overall incidence of intraventricular hemorrhage (IVH)[1] and reduce hospital mortality[2] compared with immediate cord clamping. Delayed cord clamping in preterm infants also has been shown to improve motor development at 18-22 months corrected age.[3] However, a decrease in the rate of severe IVH and improved developmental outcomes are not universally reported after placental transfusion.[1,4]

More evidence is needed on the feasibility of bedside resuscitation to allow for delayed cord clamping in compromised infants, and on the effects of umbilical cord milking before either of these approaches is considered routine.[5] Although not fully understood, animal models suggest that a reduced incidence of IVH may be explained by a smoother cardiovascular transition when ventilation precedes cord clamping.[6,7] Newborn cerebral activity and cerebral oxygenation, which may explain the differences in IVH rates, have not been previously investigated in this setting.

This study investigated how different cord clamping strategies affect preterm infants' short-term neurologic well-being and to improve our understanding of how different cord clamping strategies may affect cerebral activity and oxygenation in the first day after birth.

Methods

This prospective, randomized, controlled trial was conducted in Cork University Maternity Hospital, Ireland, between December 2015 and September 2016. Infants born at <32 weeks of gestation were eligible for inclusion. Exclusion criteria included major congenital anomaly, bleeding from placenta previa, placental abruption or accreta, twin-to-twin transfusion syndrome, hydrops, and cord prolapse. Because preterm infants have not been previously studied in this

EEG	Electroencephalogram
IVH	Intraventricular hemorrhage
NIRS	Near infrared spectroscopy

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context, a formal sample size calculation was not performed. During the 9-month study period, all infants who were assessed, met the eligibility criteria, and consented were enrolled in the study.

The study had 3 arms, immediate cord clamping, umbilical cord milking, and delayed cord clamping, with bedside respiratory support if required. Immediate cord clamping was defined as clamping the umbilicus within 20 seconds of delivery. For umbilical cord milking, the obstetrician held the infant at or below the level of the placenta and an assistant stripped the cord, 20 cm over 2 seconds, 3 times in the direction of the infant. For delayed cord clamping, infants were placed on a mobile resuscitation trolley (Lifestart, Inspiration Healthcare, Leicester, UK) with the cord intact, at or below the level of the placenta. Routine neonatal care was provided, including positive end-expiratory pressure and the provision of positive pressure ventilation if required, and the cord was clamped at 60 seconds after delivery.

All infants were wrapped in sterile towels at the time of delivery until they were transferred to the Panda Resuscitator (GE Healthcare, Laurel, Maryland). Randomization of groups was performed using a computer program and allocation concealment was achieved by using opaque, sequentially numbered, sealed envelopes. Randomization was stratified by age ($23^{0/7}$ to $27^{6/7}$ and $28^{0/7}$ to $31^{6/7}$ weeks of gestation) to ensure equal numbers of neonates born at <28 weeks of gestation in each arm. Infants born from multiple pregnancies received the same group allocation.

The Cork Teaching Hospitals' Research Ethics Committee approved this study. Antenatal written informed consent was obtained by a member of the research team before delivery. This trial was registered on the ISRCTN registry (ISRCTN92719670).

Neuromonitoring

Cerebral near infrared spectroscopy (NIRS) and electroencephalogram (EEG) monitoring commenced as soon as possible after delivery, depending on infant stability. Monitoring continued until 72 hours of age. A NIRS neonatal probe, OxyAlertTM NIRSensor (Covidien IIc, Mansfield, Massachusetts) was applied in a frontotemporal location. The EEG was recorded with the NicoletOne (CareFusion Co, San Diego, California) or Moberg (Moberg Research Inc, Ambler, Pennsylvania) EEG systems. Depending on infant size, 4-11 electrodes were used. The method for electrode placement in preterm infants in our unit previously has been described.[8] A consultant radiologist (unaware of group assignment) performed a cranial ultrasound examination within 48 hours of delivery.

Outcome Measures

The primary neonatal outcome was standard quantitative measures of preterm newborn EEG and cerebral NIRS median values collected over 1-hour time frames at 6 and 12 hours of age. The primary outcome for maternal outcome was maternal hemoglobin at 24-36 hours post partum.

Each EEG was assessed visually for overall continuity, amplitude, and symmetry and synchrony by a researcher blinded to infant randomization. EEG epochs with poor signal quality were excluded from further analysis. Multiple quantitative EEG features were computed to represent the complex waveforms of the preterm EEG.[9] An automated method removed segments of EEG corrupted by artifact,[9] before computing features on C3-C4, a common channel to all EEG recordings. The feature set comprised of spectral features, amplitude features using the range EEG, and features of the temporal organization of bursts. Spectral features are calculated within 4 frequency bands, as defined elsewhere.[9,10] The range EEG, a measure of peak-to-peak voltage, was calculated using a 1-20 Hz bandpass filter. Bursts were identified using an automated method.[10] All features were calculated using the software package NEURAL (version 0.3.3),[9] a neonatal EEG feature set in Matlab.

Cerebral oxygenation values were selected over 1-hour epochs at 6 and 12 hours of age. To remove potential artifacts caused by poor sensor contact, a 30 second collar was applied to regional cerebral oxygenation values of 15% and removed from further analysis. The median value of regional cerebral oxygenation over the hour was then used to summarize each epoch.

Echocardiographic measurements were performed on all infants at 12 ± 3 hours of age by one of the investigators who was not blinded to infant randomization. Measurements were taken according to a standard operating procedure to assess systemic blood flow, by superior vena cava flow (milliliters per kilogram per minute), right ventricular output (milliliters per kilogram per minute), and left ventricular output (milliliters per kilogram per minute). These measurements were performed offline at a later time.

Statistical Analyses

For each quantitative measure of the EEG and NIRS, simple linear regression (unadjusted analysis) was used to test for differences among the 3 groups. Because EEG and NIRS are dependent on gestational age,[11,12] a multiple linear regression (adjusted analysis) was also performed to control for this factor. In addition, linear mixed models were used to assess if the time points (6 and 12 hours) influence group differences for each quantitative EEG and NIRS feature. Gestational age, time after birth, group membership, and the interaction between group and time were set as fixed effects with the infant as a random effect. Features that were not normally distributed were log-transformed before analyses. Differences in baseline characteristics and other outcomes between the 3 groups were investigated using the Kruskal-Wallis test when the variable was continuous and the Fisher exact test when the variable was categorical.

Statistical analyses were performed using IBM SPSS Statistics version 22 (SPSS Inc, Chicago, Illinois), except for the linear mixed models, which were conducted in *R* (version 3.4.2, The R Foundation of Statistical Computing, Vienna Austria; http://www.r-project.org) using the *lme4* package (version 1.1-10). Analyses were performed on an

intention-to-treat basis. All tests were 2-sided and $P < .05$ was considered statistically significant.

Results

There were 77 infants assessed for eligibility over the 9-month study period and 45 were enrolled. Twelve infants (27%) were randomized to immediate cord clamping, 14 (31%) to delayed cord clamping with bedside resuscitation, and 19 (42%) to umbilical cord milking (**Figure 1**; available at www.jpeds.com). Uneven randomization was a result of multiple births randomized to the same intervention and a greater number of multiple births receiving umbilical cord milking. Two infants randomized to delayed cord clamping with bedside resuscitation were delivered before the research team was in place with the resuscitation trolley, and although delayed cord clamping was performed by the responsible healthcare professionals, there was no member of the research team to time the duration of delayed cord clamping; bedside resuscitation was not performed. Both infants were included in delayed cord clamping with bedside resuscitation arm for analysis on an intention-to-treat basis. There were more multiples in both the delayed cord clamping (4/14 [28.6%]) and the umbilical cord milking (13/18 [72.2%]) groups compared with the immediate cord clamping (2/12 [16.7%]) group. Infant characteristics and early secondary outcomes are provided in **Table I**.

Outcomes

There were no significant differences in the primary infant outcomes (**Table II**). There was no difference in maternal hemoglobin between groups ($P = .36$). **Table III** summarizes neonatal outcomes.

EEG Outcome. Application of EEG and acquisition of data were performed as early as possible. Seven infants had EEG monitoring commencing in the delivery room. The median age at EEG application was 3.05 hours (IQR, 1.85-5.38 hours). One infant had a very immature EEG pattern and was excluded from analysis. Data on 40 of the 44 infants (91%) were available at 6 hours and 43 of the 44 (98%) at 12 hours. **Tables IV** and **V** (available at www.jpeds.com) include a complete list of EEG features analyzed at the 6-hour and 12-hour time points. A median of 0% (IQR, 0%-0%; range, 0%-22%) of the EEG was removed by the artifact detection algorithm. No significant differences were found between the 3 groups at either time point in the unadjusted and adjusted analysis. For the linear mixed models, gestational age was significant for some (7/17) features, as was time (8/17), but not group or group-by-time interaction (0/17). **Figure 2**, A-C (available at www.jpeds.com) highlights the dependency of 3 EEG features on gestational age but not on intervention group.

NIRS Outcome. NIRS data on 40 of the 44 infants (91%) were available at 6 hours and 41 of the 44 (93%) at 12 hours. A median of 0% (IQR, 0%-0%; range, 0%-41%) of the NIRS data was removed by the artifact detection algorithm. There was no significant difference in regional cerebral oxygenation values among the 3 groups at the 6- or 12-hour time points (**Table II**). In the linear mixed model, both group and group-by-time interactions were not significant.

Secondary Outcome Measures

Although 2 infants in the immediate cord clamping group had a severe IVH compared with 1 infant in the umbilical cord milking group and no infant in the delayed cord clamping group, the difference between groups was not statistically significant ($P = .35$). There was no difference in admission temperature, mean blood pressure on admission and at 6, 12, 18, and 24 hours, or rates of bronchopulmonary dysplasia (**Table I**).

Markers for systemic blood flow based on echocardiographic measurements did not differ significantly between groups (**Table I**). The median values for superior vena cava flow were lowest in the immediate cord clamping group 50 (IQR, 47-77) and highest in the delayed cord clamping with bedside resuscitation groups 106.0 (IQR, 82.4-166.0). There were no significant differences in neonatal outcomes throughout neonatal intensive care unit stay (**Table III**).

Discussion

This prospective, randomized, controlled trial assessed short-term neurologic health in preterm infants born at <32 weeks of gestation following 3 different cord clamping strategies. There were no significant differences in cerebral oxygenation values or quantitative EEG features between groups at either 6 or 12 hours.

Until recently, immediate cord clamping had been considered the gold standard for preterm deliveries, because it allowed for immediate movement of the newborn infant to the resuscitation area for stabilization.[13] Renewed interest in the area has led to a number of randomized controlled trials and a number of meta-analyses proposing benefits for newborn infants by using alternative cord clamping strategies.[1,14-21] Also, the introduction of mobile resuscitation trolleys now allows for immediate respiratory support if required, without adverse neonatal events.[22,23] A recent meta-analysis by Fogarty et al included 18 randomized, controlled trials comparing delayed vs early clamping in 2834 infants.[2] Delayed cord clamping was found to decrease hospital mortality (risk ratio, 0.68; 95% CI, 0.52-0.90; risk difference, −0.03; 95% CI, −0.05 to −0.01; $P = .005$). However, the current evidence base is less robust than initially expected and a 2014 meta-analysis of 3 trials (n = 99) displayed no difference in neurodevelopmental outcomes at 18-24 months of age between the immediate cord clamping and the delayed cord clamping groups,[4] despite Mercer et al reporting

Table I. Infant characteristics and early secondary outcomes

Characteristics/outcomes	Immediate cord clamping (n = 12) n	Immediate cord clamping (n = 12) Median (IQR)†	Delayed cord clamping (n = 14) n	Delayed cord clamping (n = 14) Median (IQR)†	Umbilical cord milking (n = 18) n	Umbilical cord milking (n = 18) Median (IQR)†	*P* value*
Gestation (wk)	12	28.5 (25.7-30.5)	14	28 (26.4-29.6)	18	28.4 (25.7-29.6)	
Birthweight (g)	12	1080 (755-1613)	14	925 (630-1490)	18	930 (700-1545)	
Temperature (on admission)	12	36.3 (36.2-36.8)	14	36.4 (36-36.6)	18	36.6 (36.3-36.8)	.24
Hb (g/dL) 12 h	12	16.6 (15.8-17.9)	14	17.1 (16.0-18.8)	18	15.7 (14.2-17.7)	.46
MBP (mm Hg) 6 h	9	30.0 (25.5-38)	14	31.0 (27.5-33.0)	15	34 (26-37)	.41
MBP (mm Hg) 12 h	12	34.5 (31.0-40.0)	13	32 (27-36)	16	33.5 (29.0-36.8)	.50
MBP (mm Hg) 18 h	10	36.5 (32.0-42.0)	14	33.0 (29.8-37.0)	16	33.5 (30.3-39.0)	.33
MBP (mm Hg) 24 h	12	38.5 (36.3-40.8)	14	36.0 (33.5-37.3)	18	38.0 (33.0-40.3)	.22
LVO (mL/kg/min)	7	95 (89-129)	7	120 (85-156)	9	142 (67-236)	.58
RVO (mL/kg/min)	7	149 (89-174)	7	137 (136-183)	9	232.0 (92.5-442.0)	.37
SVC (mL/kg/min)	7	50 (47-77)	7	106.0 (82.4-166.0)	8	69.0 (30.0-117.8)	.11
IVH severe, n (%)	12	2 (17)	14	0 (0)	18	1 (6)	.35‡
BPD, n (%)	12	5 (42)	14	8 (57)	18	9 (50)	.70‡

Hb, Hemoglobin; *LVO*, left ventricular output; *MBP*, mean blood pressure; *RVO*, right ventricular output; *SVC*, superior vena cava.
*From the Kruskal-Wallis test unless otherwise stated.
†Unless otherwise stated.
‡From the Fisher exact test.

superior motor development in preterm infants randomized to delayed cord clamping compared with immediate cord clamping at 18-22 months of corrected age.[3]

Two large randomized, controlled trials also were inconclusive. The APTS study compared immediate cord clamping vs delayed cord clamping and found no difference ($P = .96$) in a composite outcome that included death and a number of neonatal morbidities.[24] Mortality alone was higher in the immediate group (9%) compared with the delayed group (6.4%), but this difference was not statistically significant with correction for multiple comparisons ($P = .39$). Duley et al compared cord clamping at <20 seconds with delayed cord clamping with bedside resuscitation.[22] They found a difference in death before discharge (immediate cord clamping, 11%; delayed cord clamping, 5%), but this finding was based on a small number of events with a wide CI. Also, there were no clear differences between the groups in IVH or any other serious morbidity that would potentially explain a difference in mortality. The authors concluded that further trials assessing delayed cord clamping with bedside resuscitation are urgently needed.[2,22]

Our understanding of the physiological outcomes resulting from different cord clamping strategies remains limited, and our study aimed to investigate short-term neurologic outcomes in such instances. Our study displayed nonsignificant differences in preterm infant brain oxygenation after alternative cord clamping strategies. There were no significant differences in cortical activity when measured by a comprehensive set of quantitative EEG measures. Cerebral activity and maturation did not differ between the groups, which may reflect low study numbers or, alternatively, different cord clamping strategies may not affect cerebral activity at the time points assessed in our study. In addition, we may not have identified differences that existed immediately after delivery as our primary outcomes were at 6 and 12 hours of age. Katheria et al displayed significantly lower cerebral oxygenation levels at 8-10 minutes of life in preterm infants who developed severe IVH, but did not find differences in

Table II. Comparison of EEG and NIRS among the 3 groups

EEG/NIRS	Umbilical cord milking ($n_1 = 18$; $n_2 = 18$)	Delayed cord clamping ($n_1 = 11$; $n_2 = 14$)	Immediate cord clamping ($n_1 = 11$; $n_2 = 11$)	*P* value*	*P* value Adjusted†
Burst ratio [6 h] (%)	83 (69-89)	68 (59-86)	76 (67-91)	.27	.16
Burst ratio [12 h] (%)	83 (72-93)	81 (66-90)	82 (73-89)	.95	.96
rEEG: median [6 h] (μV)	30 (21-33)	22 (18-30)	28 (22-33)	.60	.56
rEEG: median [12 h] (μV)	31 (27-37)	30 (23-40)	28 (24-34)	.61	.57
	($n_1 = 18$; $n_2 = 17$)	($n_1 = 12$; $n_2 = 13$)	($n_1 = 10$; $n_2 = 11$)		
$rcSO_2$ [6 h] (%)	83 (76-88)	85 (74-87)	87 (72-89)	.94	.97
$rcSO_2$ [12 h] (%)	80 (76-87)	81 (75-89)	79 (74-82)	.91	.88

n_1, Number of infants included at the 6-hour time point; n_2, number of infants included at the 12-hour time point; *rcSO*$_2$, regional cerebral oxygenation; *rEEG*, range EEG.
Values are median (IQR); *P* values are from the Kruskal-Wallis test.
Full list of EEG features are available in **Tables IV** and **V** online.
*From simple linear regression with group as the independent variable.
†From multiple linear regression with group and gestational age as the independent variables.

Table III. Neonatal outcomes

Outcomes	Immediate cord clamping (n = 12) n (%)*	Delayed cord clamping (n = 14) n (%)*	Umbilical cord milking (n = 18) n (%)*	*P* value†
Heart rate >100 bpm at 60 s of age	8 (66.7)	7 (50.0)	11 (61.1)	.74
Spontaneous respirations at 60 s of age	8 (66.7)	12 (85.7)	14 (77.8)	.54
Apgar at 1 minute of age: median(IQR)	6 (4.3-8.0)	6 (5-7)	5 (4.8-6.0)	.33‡
Apgar <7 at 5 minutes of age	2 (16.7)	1 (7.1)	2 (11.1)	.85
Inotropes	2 (16.7)	2 (14.3)	3 (16.7)	>.99
Neonatal blood transfusion	8 (66.7)	9 (64.3)	13 (72.2)	.92
Number of transfusions§,¶: median(IQR)	2.5 (1-3)	3 (1.3-3.0)	2 (1-4)	.89‡
Age (d) at first transfusion: median(IQR)	20.5 (7.0-28.3)	15 (3.5-39.0)	18 (5.5-27.0)	.94‡
Phototherapy	10 (83.3)	14 (100.0)	15 (83.3)	.25
Number of days on phototherapy**: median(IQR)	3.5 (2.0-7.3)	4 (2-6)	2 (2-4)	.34‡
Surfactant therapy	7 (58.3)	9 (64.3)	13 (72.2)	.73
NICU surfactant	5 (41.7)	4 (28.6)	7 (38.9)	.79
Age (h) when received NICU surfactant††: median(IQR)	1 (1-11)	1 (1.0-3.6)	2.3 (1-12)	.42‡
Mechanical ventilation	8 (66.7)	9 (64.3)	13 (72.2)	.92
Number of days on mechanical ventilation‡‡: median(IQR)	9 (2.5-29.5)	4 (2.0-13.5)	7 (5.0-36.5)	.26‡
Late sepsis	0 (0.0)	2 (14.3)	3 (16.7)	.42
Necrotizing enterocolitis	1 (8.3)	0 (0.0)	1 (5.6)	.73
Retinopathy of prematurity	0 (0.0)	1 (7.1)	0 (0.0)	.59

NICU, Neonatal intensive care unit.
Values are number (%) or median (IQR).
*Unless otherwise stated
†From Fisher exact test unless otherwise stated.
‡From Kruskal-Wallis test.
§For those who received a blood transfusion.
¶Missing data for 1 infant in the delayed cord clamping group.
**For those who received phototherapy.
††For those who received NICU surfactant.
‡‡For those who received mechanical ventilation.

brain activity or cerebral oxygenation at later times.[25] Delayed cord clamping also increases the transfer of hematopoietic stem cells, endothelial cell precursors, mesenchymal progenitors, and pluripotent lineage stem cells, which we were unable to document but may play an important role.[26]

A number of groups have evaluated NIRS in the delivery room,[27] and over the first days of life.[12,28-30] It is important to note device differences between these studies.[31] We have published delivery room data and data over the first days after birth.[12] A large study looking at NIRS data over the first day by Alderliesten et al used an adult probe with the INVOS device.[28] Our data provide similar results when the discrepancy between the probes is factored in.

There were no differences for maternal complications, neonatal stabilization interventions, or standard neonatal outcomes. This finding is important because current recommendations advise neonatal units to take part in studies assessing alternative cord clamping strategies.[5] This study highlights the feasibility of safely conducting a single-center, randomized, controlled trial with umbilical cord milking and delayed cord clamping with bedside resuscitation as experimental arms.

There are a number of limitations to this study. First, the study was not powered to an appropriate level to display superiority between cord clamping strategies based on our primary outcome measures, and numbers were too small for gestational subgroup analysis (<28 and >28 weeks of gestation). We recruited small study numbers because it was designed as a single-center study, and studies have not been previously conducted that used EEG and NIRS in similar circumstances on which to calculate sample sizes. Of note, because of the limitations in spatial EEG recording, we did not examine specific maturational features of the EEG that are known to correlate with poor outcomes, such as mechanical delta brushes and positive rolandic sharp waves.[32] Our analysis of the EEG was based entirely on the quantitative features of 1 central cerebral channel of EEG. The number of infants in each group with a comprehensive set of EEG recording electrodes was too small to analyze as a subset for this study.

Finally, some research groups now believe that there is ample evidence for the benefits of umbilical cord milking and delayed cord clamping such that immediate cord clamping should no longer be included in such studies. The recent results of the APTS and CORD trials have provided further information, which may be informative to future trials in this area.

Our study showed that there were no differences in quantitative EEG measures and cerebral oxygenation values between cord management strategies at 6 and 12 hours of age. Although our study numbers were small, our findings do add to our understanding of the short-term neurologic outcomes following different cord clamping strategies. ■

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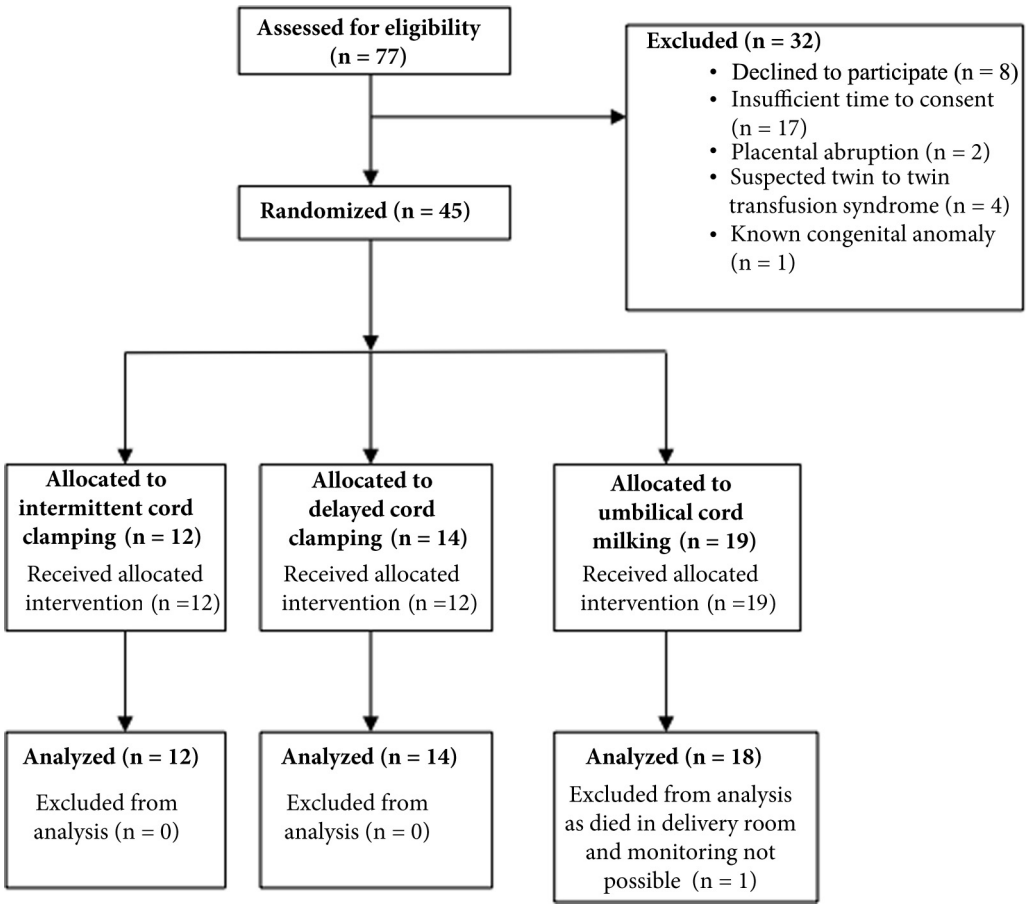

Figure 1. Flow diagram.

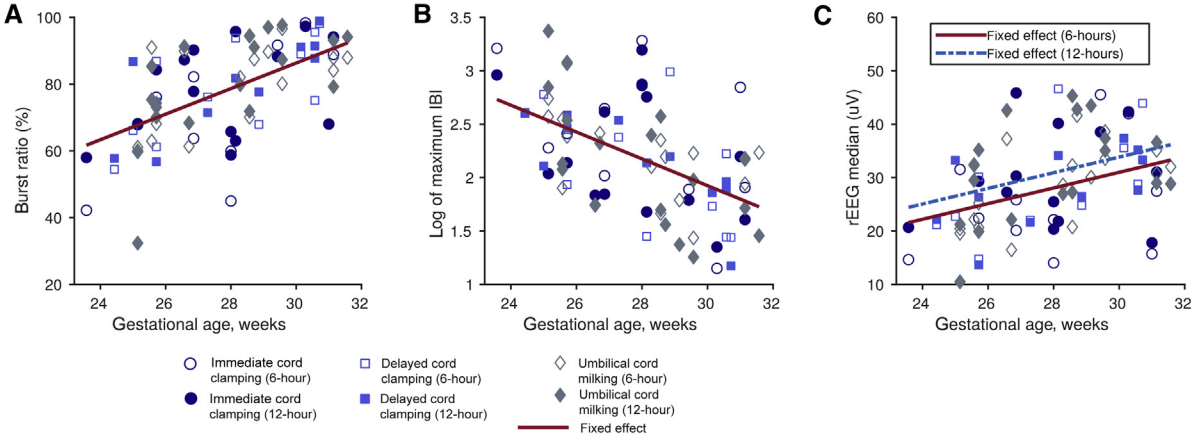

Figure 2. EEG features (**A**-**C**) highlighting the dependency on gestational age. Mixed-effect models for the 3 features included gestational age as a fixed effect (lines in **A**-**C**). Time (either the 6- or 12-hour time point) was significant ($P < .05$) in the range EEG (rEEG)-median feature plotted in **C**, but not for the features in **A** and **B**. The fixed effects of intervention group and group–time interaction were not significant ($P > .05$) and therefore are not included here.

Table IV. Quantitative EEG analysis at 6 hours after birth

qEEG features	Umbilical cord milking (n = 18) Median (IQR)	Delayed cord clamping (n = 11) Median (IQR)	Immediate cord clamping (n = 11) Median (IQR)	*P* value*	*P* value†
rEEG: median (μV)	30 (21-33)	22 (18-30)	28 (22-33)	.60	.56
rEEG: lower margin (μV)	11 (8-12)	9 (7-11)	9 (8-13)	.55	.48
rEEG: upper margin (μV)	140 (100-171)	133 (107-168)	122 (92-138)	.45	.43
Burst ratio (%)	83 (69-89)	68 (59-86)	76 (67-91)	.27	.16
Maximum IBI (s)	9.1 (6.8-11.1)	11.2 (7.1-17.3)	9.2 (5.0-12.5)	.42	.35
SP [0.5-3.0 Hz] (μV^2)	332 (313-591)	418 (206-598)	368 (231-477)	.94	.94
SP [3-8 Hz] (μV^2)	29 (18-41)	33 (17-39)	25 (12-31)	.63	.64
SP [8-15 Hz] (μV^2)	6.1 (4.8-8.6)	5.5 (4.3-9.5)	5.4 (4.0-7.6)	.85	.81
SP [15-30 Hz] (μV^2)	2.0 (1.6-2.4)	1.7 (1.2-2.6)	1.7 (1.5-2.3)	.89	.90
Relative SP [0.5-3.0 Hz] (%)	92 (91-93)	92 (91-93)	92 (91-93)	.81	.81
Relative SP [3-8 Hz] (%)	6.2 (5.1-7.0)	6.2 (5.1-7.2)	5.5 (4.9-6.4)	.75	.75
Relative SP [8-15 Hz] (%)	1.4 (1.1-1.6)	1.6 (1.0-1.8)	1.4 (1.1-2.3)	.97	.97
Relative SP [15-30 Hz] (%)	0.41 (0.38-0.68)	0.44 (0.36-0.54)	0.55 (0.40-0.84)	.70	.70
SF [0.5-3.0 Hz]	0.27 (0.24-0.30)	0.29 (0.27-0.32)	0.29 (0.26-0.33)	.98	.99
SF [3-8 Hz]	0.75 (0.72-0.78)	0.74 (0.71-0.80)	0.75 (0.74-0.81)	.75	.74
SF [8-15 Hz]	0.84 (0.80-0.85)	0.82 (0.80-0.83)	0.84 (0.80-0.87)	.30	.29
SF [15-30 Hz]	0.64 (0.63-0.69)	0.65 (0.61-0.65)	0.68 (0.64-0.69)	.28	.28

IBI, interburst interval; *qEEG*, quantitative EEG; *rEEG*, range EEG; *SF*, spectral flatness; *SP*, spectral power.
*From simple linear regression with group as the independent variable.
†From multiple linear regression with group and gestational age as the independent variables.

Table V. Quantitative EEG analysis at 12 hours after birth

qEEG feature	Umbilical cord milking (n = 18) Median (IQR)	Delayed cord clamping (n = 14) Median (IQR)	Immediate cord clamping (n = 11) Median (IQR)	*P* value*	*P* value†
rEEG: median (μV)	31 (27-37)	30 (23-40)	28 (24-34)	.61	.57
rEEG: lower margin (μV)	11 (8-13)	12 (8-13)	10 (7-12)	.77	.67
rEEG: upper margin (μV)	160 (113-194)	136 (124-188)	120 (109-138)	.38	.35
Burst ratio (%)	83 (72-93)	81 (66-90)	82 (73-89)	.95	.96
Maximum IBI (s)	8.2 (5.5-12.2)	8.1 (6.1-15.2)	8.5 (6.9-12.2)	.92	.93
SP [0.5-3 Hz] (μV^2)	579 (300-849)	461 (263-737)	394 (273-588)	.79	.79
SP [3-8 Hz] (μV^2)	33 (20-57)	27 (17-46)	19 (15-31)	.64	.65
SP [8-15 Hz] (μV^2)	6.8 (5.3-8.8)	7.5 (5.2-9.9)	6.2 (4.3-7.1)	.48	.44
SP [15-30 Hz] (μV^2)	2.3 (1.8-2.7)	2.2 (1.6-3.8)	1.9 (1.8-2.6)	.56	.55
Relative SP [0.5-3.0 Hz] (%)	93 (91-94)	93 (90-94)	93 (91-95)	.99	.98
Relative SP [3-8 Hz] (%)	5.4 (4.7-6.2)	5.5 (4.6-6.5)	4.6 (3.9-6.6)	.69	.69
Relative SP [8-15 Hz] (%)	1.1 (0.8-1.9)	1.3 (1.0-2.1)	1.0 (1.0-2.3)	.63	.53
Relative SP [15-30 Hz] (%)	0.40 (0.25-0.75)	0.43 (0.34-0.60)	0.42 (0.30-0.73)	.87	.86
SF [0.5-3.0 Hz]	0.28 (0.24-0.31)	0.29 (0.27-0.34)	0.29 (0.25-0.31)	.28	.28
SF [3-8 Hz]	0.75 (0.70-0.79)	0.76 (0.72-0.82)	0.76 (0.73-0.80)	.59	.54
SF [8-15 Hz]	0.84 (0.82-0.85)	0.83 (0.80-0.84)	0.83 (0.80-0.86)	.11	.10
SF [15-30 Hz]	0.62 (0.59-0.63)	0.63 (0.62-0.66)	0.65 (0.61-0.67)	.86	.86

IBI, interburst interval; *qEEG*, quantitative EEG; *rEEG*, range EEG; *SF*, spectral flatness; *SP*, spectral power.
*From simple linear regression with group as the independent variable.
†From multiple linear regression with group and gestational age as the independent variables.