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Cardiac and Cerebral Hemodynamics with Umbilical Cord Milking Compared with Early Cord Clamping: A randomized cluster crossover trial

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Abstract

Objective: A large, randomized cluster cross-over trial (N=1730) comparing intact umbilical cord milking (UCM) to early cord clamping (ECC) in non-vigorous near-term/term newborns demonstrated a reduction in cardiorespiratory interventions at birth and less moderate to severe hypoxic ischemic encephalopathy. We evaluated changes in cerebral tissue oxygenation (StO_2), pulse oximetry (SpO_2), pulse rate and fraction of inspired oxygen (FiO_2) during the first 10 minutes of life in a subset of infants enrolled in the parent trial.

Study design: Infants enrolled in the Milking in Non-Vigorous Infants trial that had StO_2 monitoring at birth were included in the sub-study conducted at 3 hospitals the US and Canada. A near-infrared spectroscopy sensor, pulse oximeter and electrocardiogram electrodes were placed. Pulse rate, StO_2, SpO_2, and FiO_2 were collected for the first 10 minutes after birth. Longitudinal models were used to compare effects of UCM and ECC.

Results: Thirty-four infants had StO_2 data. Fifteen of these infants received UCM and 19 had ECC. Infants receiving UCM had similar heart rates, SpO_2, and StO_2 values, but were exposed to less FiO_2 over the first 10 minutes of life than infants with ECC (0.26±0.12 vs. 0.81±0.05 at 10 minutes).

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Author Statement

Anup Katheria: Conceptualization, Funding acquisition, writing original draft preparation. **Brenda Law**: Writing- Reviewing and Editing. **Debra Poeltler**: Formal Analysis, Writing- Formal Analysis Reviewing and Editing **Georg Schmoelzer**: Writing- Reviewing and Editing. **Wade Rich**: Writing- Reviewing and Editing. **Felix Ines:** Writing- Reviewing and Editing. **Satyan Lakshminrusimha**: Writing- supervision, Reviewing and Editing.

Data sharing statements: Data will be available after the primary follow-up paper is published. Individual participant data (including data dictionaries) will be available upon review by the study PI.

Study was presented as a poster at the Pediatrics Academic Society Meeting, Denver, CO April 2022.

Conclusion: Non-vigorous term/near term infants who received UCM at birth required lower FiO_2 after delivery when compared to infants who umbilical cords were clamped soon after birth while achieving similar peripheral and cerebral oxygenation. Cord milking may be a potential option for placental transfusion in non-vigorous near term/term infants when delayed cord clamping cannot be performed.

Keywords

oxygen; delayed cord clamping; early cord clamping; hypoxic ischemic encephalopathy

Introduction:

The current practice for term newborn infants without immediate need for resuscitation is to delay the clamping and cutting of the umbilical cord by at least 30 seconds. (1)This practice is supported by randomized controlled trials and meta-analyses, and several governing bodies endorse delayed cord clamping (DCC). (2–4) Implementing DCC is particularly difficult in the non-vigorous infant, due to the perceived need for immediate respiratory support with concerns that delayed resuscitation may lead to prolongation of hypoxia and bradycardia. In these infants, umbilical cord milking (UCM) may have advantages over early cord clamping (ECC) by allowing placental transfusion without delaying resuscitation. We recently demonstrated that UCM reduced the need for cardiorespiratory resuscitation at birth and decreased the incidence of moderate to severe hypoxic-ischemic encephalopathy (HIE) in non-vigorous term and near-term infants.(5)

The influence of placental transfusion on cerebral oxygenation in non-vigorous infants is unknown. Observational data from vigorous term infants provide normative cerebral oxygenation values, with both cerebral hypoxia and hyperoxia hypothesized to be contributory to brain injury. (6)Previous observational data have shown an association between elevated cerebral oxygenation values and the development of brain injury and poor longer-term outcomes in non-vigorous infants with HIE. (7, 8)

We recently reported results from a multicenter trial (N=1730, 10 centers) comparing UCM to early cord clamping (ECC) in non-vigorous infants at $35–41^{6/7}$ weeks gestation (milking in non-vigorous infants -MINVI trial – NCT03631940). Outcomes demonstrated that patients with UCM had less need for cardiorespiratory support at delivery, improved 1 minute Apgar score, higher hemoglobin levels, lower incidence of moderate-to-severe hypoxic-ischemic encephalopathy (HIE) and less need for therapeutic hypothermia. (5) As part of the MINVI trial, we conducted a sub-study that included additional hemodynamic investigations involving advanced delivery room monitoring and collection of delivery room data. Specifically, we sought to evaluate the changes in cerebral tissue oxygenation (StO_2), peripheral arterial oxygenation (SpO_2) measured by oximetry, heart rate, and the fraction of inspired oxygen (FiO_2) during the first 10 minutes of life in infants randomized to either ECC or UCM. Based on studies in term infants showing higher SpO_2 with DCC, we hypothesized that infants receiving UCM would have higher cerebral and systemic oxygenation in the first 10 minutes of life. (9, 10)

Methods

Non-vigorous infants enrolled in the parent MINVI trial at 3 of 10 MINVI centers (Sharp Mary Birch Hospital for Women & Newborns, Sharp Grossmont Hospital, and Royal Alexandra Hospital in Edmonton, Alberta) were eligible for the near-infrared spectroscopy (NIRS) sub-study. Briefly, the MINVI trial was a pragmatic cluster-randomized crossover trial of infants between 35–41 $^{6/7}$ weeks (figure 1). (5) Centers were randomized to UCM (milking the intact cord 4 times) or ECC (clamping < 60 seconds after birth) for one year and then crossed over to the other arm for an additional year. Computer generated randomization of sites was performed once ethics approval was obtained. This sub-study was approved at the Sharp Institutional Review Boards and the Research Ethics Board in Edmonton, Alberta.

Cerebral tissue oxygenation using near infrared spectroscopy (NIRS) was collected for the first ten minutes after birth in three Level III neonatal intensive care units located in the USA and Canada. The inclusion criteria were: 1) enrollment in the main MINVI trial (gestational age ≥ 35 weeks, deemed non-vigorous at birth, received study intervention, and obtained post-intervention parental consent) and 2) NIRS data available within 10 minutes after birth. Once the infant was assigned to the intervention (UCM or ECC), 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, and FiO_2 were collected for 10 minutes in the delivery room. Neonatal resuscitation proceeded in accordance with Neonatal Resuscitation Program 7th edition, with time-based preductal SpO_2 targets (shaded area in figure 2C). (11) Although SpO_2 and heart rate data were available to the clinical team, data from NIRS was blinded to practitioners and did not influence resuscitation. 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 CA) in the delivery room at Sharp Mary Birch Hospital and Sharp Grossmont Hospital. A respiratory profile monitor (NM2, Phillips Healthcare, Electronics Ltd. Markham, ON, Canada) was used at the Royal Alexandra Hospital in Edmonton, Alberta, Canada. Data 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.

HIE was categorized as mild, moderate and severe using the highest Sarnat stage documented in the first six hours of life. (12) All sites agreed to strictly follow and document the level of HIE.

As this was a pilot study there was no power calculation available to estimate sample size, we present the available data here.

Statistical Analyses

Descriptive statistics were calculated by treatment group for maternal and neonatal baseline characteristics and 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. Two sample t-tests were used to compare the mean differences between UCM and ECC groups for each minute increment for NIRS, pulse rate, StO_2, and FiO_2 measures. Longitudinal models fit by generalized estimating equations (GEE) were used to assess differences between UCM and ECC for NIRS, pulse rate, StO_2, SpO_2, and FiO_2 measures in the first 10 minutes after birth. Statistical hypothesis tests were evaluated at a 0.05 alpha level and no adjustments for multiple testing were performed. SPSS version 24 (Armonk, NY: IBM Corp.) was used for all analyses.

Results

Thirty-four infants who were enrolled in the parent MINVI trial and randomized had data tracings at birth January 2019 through May 2021. Of these infants, 15 received UCM and 19 had ECC (see Figure 1, CONSORT). The maternal demographics and neonatal outcomes are shown in Table 1 and Table 2, respectively. There were no differences in maternal characteristics or neonatal outcomes apart from onset of spontaneous labor or uterotonics prior to delivery. No statistical differences were observed between UCM and ECC for heart rate or SpO_2 for each minute increment using t-tests or longitudinally estimated by GEE modeling. Minute increment comparison between UCM and ECC for NIRS and FiO_2 are shown in Figure 2. Infants in the ECC group needed rapid escalation of FiO_2 (figure 2B). Overall differences between UCM and ECC estimated by GEE models were only significant for FiO_2 (p=.01, OR .925, 95% CI .872, .982).

Discussion

Current neonatal resuscitation guidelines recommend continuous monitoring of heart rate and preductal SpO_2 for infants requiring resuscitation, with set targets for heart rate and SpO_2. The goal of neonatal resuscitation is to ventilate the lungs and provide adequate oxygen to tissues while minimizing oxygen toxicity. (13) An increasing heart rate and SpO_2 are signs of effective resuscitation and are surrogate markers of blood flow and oxygen delivery to vital organs such as the brain. Measurement of cerebral tissue oxygenation (StO_2) is an additional tool to assess brain perfusion and oxygenation. Resuscitation strategies that achieve optimal cerebral oxygenation at the least possible inspired oxygen have the potential to minimize systemic and pulmonary oxygen toxicity.(13)

Both cerebral hypoxia and hyperoxia has been hypothesized to contribute to neonatal brain injury. (14, 15) Unlike preterm infants where *decreased* cerebral oxygenation values both in the NICU and delivery room are correlated with brain injury such as intraventricular hemorrhage (16), term HIE infants with *increased* cerebral oxygenation values in the first 72 hours have been associated with poorer neurodevelopmental outcomes.(7, 8)

However, there are limited NIRS studies of term infants in the delivery room (17), and none have evaluated different cord management strategies in non-vigorous infants. Umbilical

venous blood has an oxygen saturation of approximately 80–85% and placental transfusion by DCC or UCM provides a bolus of oxygenated blood to the neonate. (18) Our data suggest that non-vigorous infants receiving UCM received lower amounts of supplemental oxygen at birth when compared with infants receiving ECC, while achieving similar heart rate, SpO_2 and more importantly cerebral oxygenation. Lower FiO_2 requirements could have been due to infusion of oxygenated umbilical venous blood, improved systemic perfusion or higher pulmonary blood flow from increased placental transfusion. Despite higher inspired oxygen in the ECC group, both systemic (SpO_2) and cerebral tissue (StO_2) oxygen saturations were similar between groups, suggesting that oxygen saturations were kept within oxygen target ranges in the ECC group by exposing the infant to significantly higher inspired oxygen concentrations potentially increasing the risk of pulmonary oxygen toxicity. (19)

Kaempf et al have demonstrated that preterm infants receiving a placental transfusion from DCC had less need for supplemental oxygen and less mask ventilation compared to infants with ECC. (20) Our group has previously reported the effects umbilical cord milking on the need for oxygen administration in a prior randomized controlled trial of preterm infants in the delivery room. (21) Infants receiving UCM had higher heart rates, higher SpO_2, and were exposed to less FiO_2 in the delivery room compared to those receiving early cord clamping at birth. However, while the delivery room benefits have been consistently seen with UCM in preterm infants, it is associated with an increase in severe IVH. (22) Term and near-term infants do not have the same risk for IVH as preterm infants, and for non-vigorous term infants where DCC may delay resuscitation, placental transfusion from UCM may be beneficial, as they are at higher risk for hypovolemia. This was previously demonstrated by Linderkamp et al, who used biotin-tagged red blood cells to measure blood volume in term infants. (23) In this study, following vaginal delivery, infants with lower Apgar scores (<5) at 5 minutes of age had lower blood volume compared to those with higher (>5) Apgar scores.

Placental transfusion whether from DCC or UCM potentially improves pulmonary blood flow by the addition of oxygenated placental blood. The decreased need for supplemental oxygen supports the concept that in non-vigorous infants who may also be hypovolemic, enhancing pulmonary transition at birth by increasing pulmonary blood flow earlier may lead to less oxygen need. This speculation also explains the decreased need for cardiopulmonary resuscitation observed with UCM in the parent MINVI Trial. (5)

This study has several limitations. This study included only a small subgroup of infants in level III NICUs within the MINVI trial. However, these infants were at high risk as shown by the high incidence of (12/34) HIE in this cohort. We were unable to blind the intervention at the time of delivery; the neonatal team was in the same room as the parent and could see the intervention (milking or early cord clamping) and theoretically there could have been bias in the data collected. However, the primary outcome for the MINVI trial was admission to the NICU, and the SpO_2, heart rate, StO_2 and FiO_2 data were collected for a secondary analysis. Neonatal providers were adjusting FiO_2 based on preductal SpO_2 and the clinical status of the infant.

Conclusion

Non-vigorous term/near term infants who receive UCM at birth require lower concentrations of inspired oxygen after birth when compared to infants whose umbilical cords are clamped soon after birth while achieving similar peripheral and cerebral oxygenation. Intact cord milking appears to be an effective strategy to enhance cerebral and systemic oxygenation while limiting pulmonary oxygen exposure. Hence in non-vigorous near term/term infants, UCM offers an alternate approach for placental transfusion when delayed cord clamping is not ideal due to immediate need for resuscitation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

UCM	Umbilical cord milking
ECC	Early cord clamping
HIE	Hypoxic ischemic encephalopathy
FiO_2	Fraction of Inspired Oxygen
StO_2	Cerebral Oxygenation

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Highlights

- Non-vigorous term/near term infants who receive umbilical cord milking at birth require less supplemental oxygen at birth.
- There was no difference in cerebral or systemic oxygenation at birth between umbilical cord milking and early cord clamping.
- Cord milking may be a potential option for placental transfusion in non-vigorous near term/term infants when delayed cord clamping cannot be performed.

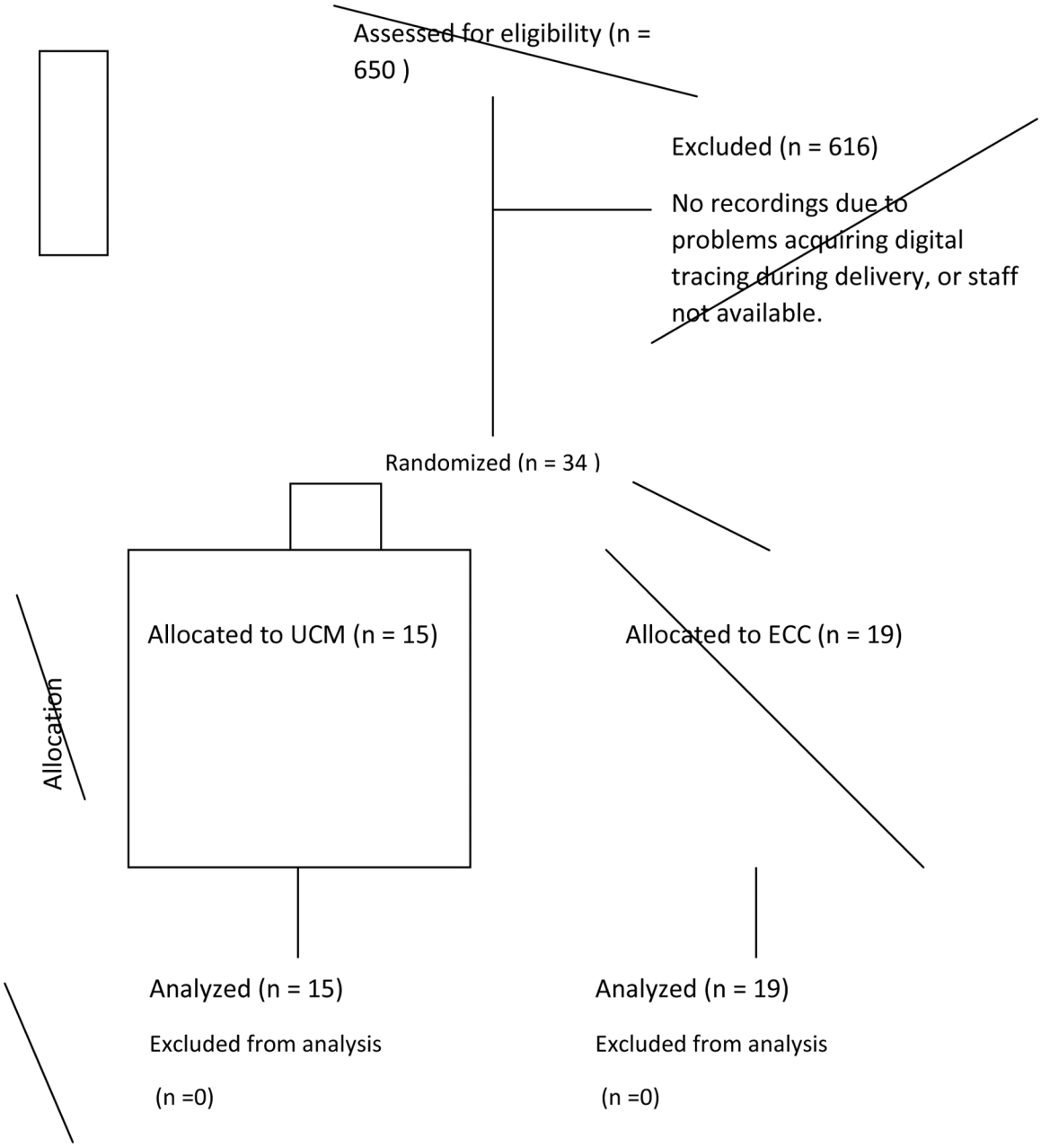

FIGURE 1.
CONSORT DIAGRAM: MINVI NIRS SUBSTUDY

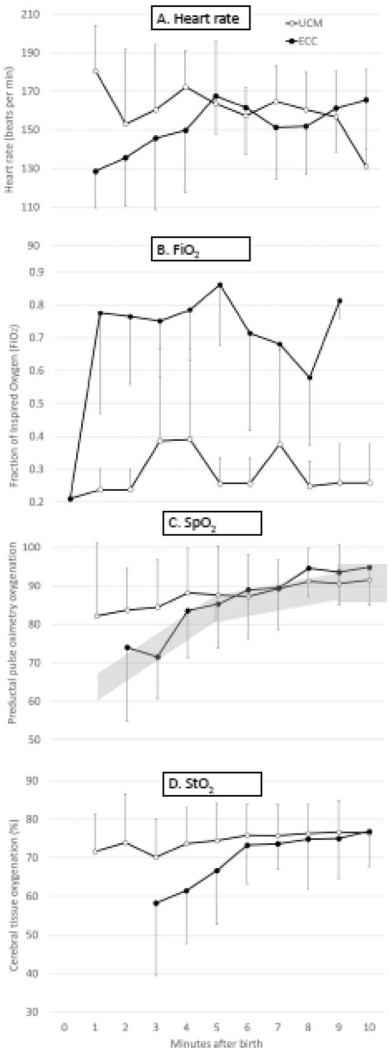

Figure 2.

Graphic display of heart rate (A), fraction of administered inspired oxygen (FIO_2 - B) preductal oxygen saturations (SpO_2), and cerebral oxygenation (StO_2), during the first 10 minutes after birth by groups (UCM: umbilical cord milking, ECC: early cord clamping). The shaded area in figure C indicates SpO_2 target as recommended by the American Academy of Pediatrics – Neonatal Resuscitation Program.

Table 1.

Maternal and Infant Characteristics

	Umbilical cord milking N=15	Early cord clamping N=19	Mean difference	p value
Maternal age, y (mean, sd)	33 ± 5	29.5 ± 4.5	3.4	0.064
Birth gestational age, wk (mean, sd)	38.13 ± 1.56	38.95 ± 1.72	0.568	0.162
Female (n,%)	6 (40)	10 (53)		0.464
Cesarean Delivery (n,%)	9 (60)	9 (47)		0.464
Maternal Diabetes (n,%)	2 (13)	2 (11)		0.99
Maternal Chorioamnionitis (n,%)	0	5 (26)		0.053
Pregnancy-induced hypertension/preeclampsia (n,%)	5 (33)	2 (11)		0.199
Labor or uterotonics before delivery (n,%)	9 (60)	17 (90)		0.012
Duration of rupture of membranes before delivery, h (median, IQR)	0 (0,10)	5 (0,13)		0.372
General anesthesia (n,%)	0	1 (5)		0.99
Small for gestational age (n,%)	0	2 (11)		0.49
Multiple gestation	1	2		0.99

Table 2.

Neonatal outcomes by treatment group

	Umbilical cord milking n=15	Early Cord clamping n=19	Mean difference	p value
Death prior to hospital discharge	0	0		n/a
Hemoglobin at 12–48 h (g/dL)	17 ± 3	16 ± 3	1.389	0.39
Hematocrit at 12 – 48 h (%)	49 ± 9	46 ± 9	2.8	0.56
Types of support in delivery room				
None	6	3		0.139
Supplemental oxygen	9	16		0.139
Positive pressure ventilation	5	10		0.484
Continuous positive airway pressure	7	6		0.367
Intubation	0	0		
Peak serum bilirubin (mg/dL)	10 ± 4	8.69 ± 5	1.381	0.546
Phototherapy	2	4		0.672
Transfusion (during NICU stay)	0	1		0.999
Therapeutic hypothermia	0	4		0.113
HIE (any)	3	9		0.151
Mild	3	5		0.99
Moderate	0	3		0.237
Severe	0	1		0.99
Admission mean blood pressure (mmHg)	42 ± 8	46 ± 4	−4.679	0.199
Venous cord gas pH	7.25 ± .11	7.22 ± .10	0.027	0.553
Venous cord gas base excess (mEq/L)	−7 ± 3	−8 ± 4	1.26	0.438
Arterial cord gas pH	7.17 ± .11	7.09 ± .18	0.073	0.276
Arterial cord gas base excess (mEq/L)	−7 ± 4	−11 ± 6	3.43	0.147