A Randomized Clinical Trial of Umbilical Cord Milking vs Delayed Cord Clamping in Preterm Infants: Neurodevelopmental Outcomes at 22-26 Months of Corrected Age

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Objective To compare the effect of umbilical cord milking vs delayed cord clamping (DCC) on neurodevelopmental and health outcomes in very preterm infants at 22-26 months of corrected age.

Study design Neurodevelopmental outcomes at 2 years of age were assessed using the Bayley Scales of Infant Development, third edition, and a standardized neurologic examination. Data regarding pulmonary morbidities, neurosensory impairments, and hospitalizations were obtained by parental interview. Intention-to-treat was used for primary analyses.

Results Of the 197 infants enrolled in the original study there were 15 deaths, 5 in the umbilical cord milking group and 10 in DCC group. Of the remaining infants, 135 (74%) were assessed at 22-26 months of corrected age. Demographics in umbilical cord milking (n = 70) and DCC (n = 65) groups were similar. Infants randomized to umbilical cord milking at birth had significantly higher cognitive and language composite scores, and were less likely to have a cognitive composite score of <85 (4% vs 15%; $P = .04$). Motor function was similar in both groups. There were no differences in the incidences of mild or moderate to severe neurodevelopmental impairment, hearing or visual impairments, pulmonary morbidities, or rehospitalizations between the 2 groups.

Conclusions Infants randomized to umbilical cord milking had higher language and cognitive scores compared with those randomized to DCC. There was no difference in rates of mild or moderate to severe neurodevelopmental impairment. *(J Pediatr 2017;■■:■■-■■).*

Trial registration clinicaltrials.gov NCT01434732.

Providing a placental transfusion to preterm newborns is now standard practice. Recently the American College of Obstetricians and Gynecologists endorsed delayed cord clamping (DCC) for full-term newborns, adding to the prior recommendation for premature newborns.[1] However, because DCC delays transfer to the resuscitation team, milking of the umbilical cord (gently squeezing the intact umbilical cord from the placental side toward the neonatal umbilicus several times before it is clamped) could provide a placental transfusion in preterm newborns who require immediate resuscitation. Recently, the European consensus statement has suggested umbilical cord milking can be considered as an alternative when DCC clamping cannot be performed.[2] However, the current recommendation by the International Liaison Committee on Resuscitation is, "against the routine use of cord milking for infants born at less than 29 weeks of gestation outside of a research setting."[3]

Long-term neurodevelopmental outcome data are needed demonstrating the safety and/or efficacy of umbilical cord milking before changes in the recommendations can be made. Our previous, randomized, controlled, prospective trial comparing umbilical cord milking with DCC demonstrated that umbilical cord milking provided a higher volume placental transfusion, higher superior vena cava flow, and better cardiac function at 12 hours of life in premature newborns born by Cesarean delivery at <32 weeks of gestation.[4] For this pilot study, we hypothesized that umbilical cord milking, compared with DCC, would result in better neurodevelopmental outcomes at 22-26 of months corrected age (CA).

Methods

This prospective, randomized, controlled intervention trial comparing the neonatal outcomes following umbilical cord milking vs DCC was conducted between August 2013 and August 2014 at 2 tertiary centers (Sharp Mary Birch Hospital

Bayley-III	Bayley Scales of Infant and Toddler Development, third edition
CA	Corrected age
DCC	Delayed cord clamping
GMFCS	Gross Motor Function Classification System

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for Women and Newborns and Loma Linda University Medical Center). The institutional review board and ethics review board at both sites approved the study and consent. The consent for this trial (ClinicalTrials.gov: NCT01866982) included neurodevelopmental follow-up at 2 years of age (22-26 months of CA). Trial entry criteria included a gestational age of $23^{0/7}$-$31^{6/7}$ weeks. Multiples (twins or triplets) received the same treatment assignment. Exclusion criteria included monochorionic multiples, incarcerated mothers, placenta previa, concern for placental abruption, Rh sensitization, hydrops, and congenital anomalies. Women in labor with fetuses at <32 weeks of gestation were randomized using computer-generated allocation with sealed envelopes before delivery to either umbilical cord milking (milking the cord by squeezing the cord toward the infant over 2 seconds and repeating 3 additional times before clamping and cutting the cord) or DCC (delayed clamping and cutting of the umbilical cord after 45-60 seconds).

Neonatal clinical outcomes of the original cohort were published previously, including the admission hemoglobin drawn shortly after birth, need for inotropic medications for hypotension, intraventricular hemorrhage, congenital sepsis, and bronchopulmonary dysplasia.[4] These outcomes were reported herein for the subjects receiving neurodevelopmental follow-up.

The primary neurodevelopmental outcomes for this study were cognitive, motor, and language function at 22-26 months of CA. Secondary outcomes included neurologic impairment, measurements, pulmonary morbidities, and rehospitalizations. All visits at 22-26 months of CA were funded by the study. Families were given reimbursement for travel including gas, airfare, and/or hotel expenses if they lived out of state or a long distance from the study site.

The 22- to 26-month CA follow-up visit included a health history, physical examination, and cognitive, language, and motor assessment using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III),[5] a standardized neurologic examination, and measurements (weight, length, and head circumference). The Gross Motor Function Classification System (GMFCS) was used to evaluate functional motor outcome. Neurodevelopmental assessment was carried out by examiners who were trained in administration of the Bayley-III, had excellent inter-rater reliability (0.90), and masked to the umbilical cord milking or DCC status. The Bayley-III includes Cognitive, Language (receptive and expressive subscales), and Motor (fine and gross motor subscales) composite scores with a mean and SD of 100 ± 15. The GMFCS, as modified by the National Institute of Child Health and Human Development Neonatal Research Network, is a validated system can be used for children between 22 and 26 months of CA to describe the severity of motor dysfunction.[6] GMFCS levels range from 0 to 5 with a level of 1 indicating mild impairment and a level of 5 indicating the most severe motor impairment. Data regarding visual (eg, eye surgery, strabismus, myopia) or hearing impairments, pulmonary morbidity including the need for oral or inhaled steroids, oxygen, and bronchodilators, and rehospitalizations were obtained by parental interview.

Moderate to severe neurodevelopmental impairment was defined having ≥1 of the following: a Cognitive composite score of <70, GMFCS of ≥2, blindness (vision of <20/200), or hearing impairment interfering with the ability to communicate with amplification.[7] Mild neurodevelopmental impairment was defined as having a Cognitive score of 70-84, GMFCS score of 1, unilateral blindness (vision of 20/200 in only 1 eye), or hearing impairment or need for hearing aids that does not interfere with the ability to communicate.[7]

Statistical Analyses

This study was a secondary outcome of the overall trial that was powered to detect a difference in a measure of systemic blood flow (ie, superior vena cava flow).[4] Based on a recent study comparing cord milking with DCC that reported higher Language composite scores (108 ± 18 vs 95 ± 21) with cord milking on the Bayley-III,[8] we determined that an estimated sample size of at least n = 63 per group (total n = 126) would be needed to detect at least an absolute difference of 10 points with a 2-sided alpha of 0.05 and 80% power (SPSS Sample Power, IBM, v. 3.01, SPSS Inc, Chicago, Illinois). This sample size allowed for a 25% attrition rate for children lost to follow-up or death before discharge. Continuous variables were analyzed using Student *t* tests and categorical variables were analyzed using χ^2 tests.

Using linear regression modeling, the following independent variables were considered as potential predictors of Bayley-III Cognitive, Language and Motor composite scores: randomization group (DCC vs umbilical cord milking), public vs nonpublic insurance as a surrogate for socioeconomic status, gestational age, birth weight, vaginal vs cesarean delivery, and head circumference, height, and weight at follow-up. Variables were examined for model assumptions including normality, independence, linearity, and homoscedasticity. Individual observations were examined for outliers, leverage, and influence. The predictor variables were examined for collinearity using variance inflation factors and tolerance values. Variables with *P* values of <.2 in univariate analyses and others thought to be important based on previous research were considered for inclusion in the modeling procedures. Regression coefficients and F tests were used to evaluate variables in and out of each model to obtain the final reduced models and best model fit. Although gestational age and birth weight were highly correlated, only gestational age was retained for consideration in further modeling.

Results

Of the 197 infants enrolled in the original study, there were 15 deaths, 5 in the umbilical cord milking group and 10 in the DCC group (**Figure**). Of the remaining infants, 135 (74%) were assessed at 22-26 months of CA. There were no differences in demographics or perinatal outcomes between the umbilical cord milking and DCC groups (**Table I**). Compared with children seen for follow-up, children lost to follow-up were born to younger mothers (28 ± 6 years of age vs 30 ± 5 years of age;

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