The Effects of Umbilical Cord Milking on Hemodynamics and Neonatal Outcomes in Premature Neonates

Anup C. Katheria, MD[1], Tina A. Leone, MD[2], Doug Woelkers, MD[3], Donna M. Garey, MD[4], Wade Rich, RRT[1], and Neil N. Finer, MD[1,4]

Objective To determine whether umbilical cord milking (UCM) improves systemic blood flow and reduces neonatal morbidities compared with immediate cord clamping (ICC).

Study design Women admitted to a tertiary care center and delivering before 32 weeks' gestation were randomized to receive UCM or ICC. Three blinded serial echocardiograms were performed in the first 2 days of the infant's life. The primary outcome was measured systemic blood flow (superior vena cava flow) at each time point.

Results Of the 60 neonates who were enrolled and randomized, 30 were assigned to cord milking and 30 to ICC. Neonates randomized to cord milking had greater measures of superior vena cava flow and right ventricular output in the first 6 hours and 30 hours of life. Neonates receiving UCM also had greater serum hemoglobin, received fewer blood transfusions, fewer days on oxygen therapy, and less frequent use of oxygen at 36 weeks' corrected postmenstrual age.

Conclusions We demonstrate greater systemic blood flow with UCM in preterm neonates compared with ICC. Future large prospective trials are needed to determine whether UCM reduces intraventricular hemorrhage and other long-term morbidities. *(J Pediatr 2014;164:1045-50)*.

One possible mechanism of intraventricular hemorrhage (IVH) is hypoperfusion of the brain in the first hours of life, which then leads to IVH hours-to-days later, after perfusion has stabilized. Kluckow and Evans[1] demonstrated an association between low perfusion and the subsequent development of IVH. In this study, low perfusion was defined as low superior vena cava (SVC) flow and measured by functional echocardiography (<30, 34, 42, and 46 mL/kg/min, respectively, at 5, 12, 24, and 48 hours of age).[1] The current evidence demonstrates that SVC flow is a predictor of impaired long-term neurodevelopmental outcomes at 3 years of age independent of the development of IVH.[2] Improving SVC flow by cord milking could potentially be a mechanism of improving subsequent neurodevelopment. Unfortunately, there are currently no interventions that have been shown to prevent or improve low SVC flow in preterm neonates at risk for neurologic impairment.[3-5]

Umbilical cord milking (UCM), in which the unclamped umbilical cord is milked before it is clamped, may influence SVC flow by improving perfusion immediately after birth. During the first 30 seconds after delivery, blood volume in the newborn increases by 12 mL/kg.[6] This early placental transfusion does not occur if the cord is clamped immediately. Recently, the American College of Obstetricians and Gynecologists recommended a 30- to 60-second delay in umbilical cord clamping for all preterm deliveries.[7] Investigators from one randomized controlled trial and a historical controlled trial of delayed cord clamping (DCC) have demonstrated that DCC is associated with increased SVC flow compared with immediate cord clamping (ICC).[8,9] Although DCC increases SVC flow and decreases the overall incidence of IVH, the enthusiasm for DCC is tempered by the delay in resuscitation. UCM results in rapid blood transfer from the placenta to the newborn, allowing for resuscitation to take place quickly. A retrospective study of UCM compared with ICC suggested SVC flow could in part be improved by UCM.[10] To our knowledge, there has not been a randomized controlled trial in which investigators evaluated the effects of UCM on systemic blood flow. We hypothesized that UCM could improve perfusion, or systemic blood flow, in preterm neonates as measured by SVC flow and right ventricular output (RVO) and would be associated with decreased neonatal morbidities compared with ICC.

BP	Blood pressure	OB	Obstetrician
DCC	Delayed cord clamping	PDA	Patent ductus arteriosus
FO	Foramen ovale	PMA	Postmenstrual age
Hct	Hematocrit	RVO	Right ventricular output
ICC	Immediate cord clamping	SVC	Superior vena cava
IVH	Intraventricular hemorrhage	UCM	Umbilical cord milking
LVO	Left ventricular output		

From the [1]Department of Neonatology, Sharp Mary Birch Hospital for Women and Newborns, San Diego, CA; [2]Division of Neonatology, Department of Pediatrics, Colombia University, New York, NY; and [3]Division of Perinatology, Department of Obstetrics and [4]Division of Neonatology, Department of Pediatrics, University of California San Diego, San Diego, CA

The authors declare no conflicts of interest.

Registered with ClinicalTrials.gov: NCT01434732.

 http://dx.doi.org/10.1016/j.jpeds.2014.01.024

Methods

This randomized, controlled trial was conducted at a single tertiary care center and was approved by the Institutional Review Board at University of California, San Diego. Pregnant women dated by their earliest ultrasound or last menstrual period at <32 weeks' gestation were identified and recruited. Pregnant women who on admission were considered to have imminent delivery were not approached. Additional exclusion criteria included monochorionic multiples, incarcerated mothers, placenta previa, concern for abruptions, or refusal to perform the intervention by the obstetrician (OB). Given that depressed infants who required resuscitation could potentially benefit from an initial placental transfusion because of their increased risk for adverse outcomes, the investigators did not exclude infants who had nuchal cords or the need for resuscitation. Entry criteria included a gestational age of 23 0/7 to 31 6/7. Infants were randomized by the placement of their information in opaque, sealed envelopes immediately before delivery, with stratification by gestational age (23-28 6/7 or 29-31 6/7). The OBs were made aware of the randomization by the neonatology team before delivery of the infant. Using the wall-mounted clocks in the delivery room, the neonatal fellow attending the delivery recorded the time elapsed from when the infant was delivered until the time the umbilical cord was clamped by the OB in both arms of the study. UCM was performed by having the delivering OB hold the infant below the mother's introitus at vaginal delivery or below the level of the incision at cesarean delivery and having the assistant (the second OB) milk about 20 cm of umbilical cord over 2 seconds (counting aloud), repeating 2 additional times as described previously.[11]

Blinded serial echocardiographic examinations were performed for all neonates in the first 6 hours, between 12 and 24 hours, and between 24 and 36 hours of life with the Vivid E9 cardiovascular ultrasound system with a 12S phased-array transducer (GE Medical Systems, Milwaukee, Wisconsin). Although the target times for the second and third echocardiograms were 18 and 30 hours, respectively, there was a margin of plus or minus 6 hours. All neonates had a bedside head ultrasound to document evidence of IVH in the first 6 hours of life. Formal head ultrasounds were performed on the second or third day of life.

Echocardiograms and head ultrasounds were performed mainly (>90%) by the principal investigator (A.K.). If he was not available, one of the coinvestigators (T.L., D.G.) completed the examinations. None of the investigators performing echocardiograms were involved in the randomization or the recording of the intervention. All images were analyzed and measured offline by use of the EchoPAC software (GE HealthCare, Horten, Norway) and were analyzed without knowledge of the assigned group by the principle investigator. The blinding was possible by allowing only the neonatal fellow attending the delivery and the OB performing the intervention to be aware of the allocation arm. No documentation of the intervention was made in the delivery record. The randomization cards assigned a subject identification number that was kept by the research coordinator.

Measures of SVC flow, RVO, left ventricular output (LVO), diameter and direction of flow through the patent ductus arteriosus (PDA), and diameter and direction of flow through the foramen ovale (FO) were obtained on each examination. Flow measures were calculated by the diameter of the blood vessel, the velocity time integral from the pulse wave Doppler signal, and heart rate with the following formula:

$$\text{cross-sectional area} \times \text{velocity time integral} \times \text{heart rate}/8\ (\text{kg})$$

as previously described.[12-14] Blood pressure (BP), heart rate, and transcutaneous CO_2 also were documented at the time of each examination. The primary outcome was the SVC flow for the 3 time points.

A single study-related blood draw (hematocrit [Hct] at 12 hours from a central line or venipuncture) and neonatologist-performed head ultrasound (the first scan <6 hours of life) were collected as part of the research protocol. Admission complete blood count and head ultrasounds on the second or third day of life were part of routine care. All other relevant prenatal and neonatal data were obtained from the medical records of mother and infant.

Statistical Analyses

On the basis of our own retrospective review of SVC flow measures performed in premature neonates who developed IVH compared with those who did not, a sample size calculation determined at least 30 neonates in each group were required to demonstrate at least a 25% difference in SVC at 6 hours between neonates treated with UCM compared with ICC with a 2-sided alpha of 0.05 and 80% power. Statistics were performed using PASW Statistics 18.0 (PASW Statistics, Chicago, Illinois). Normally distributed continuous outcome variables were compared with the unpaired Student *t* test, and nonparametric continuous outcome variables were analyzed with the Mann-Whitney *U* test. Comparisons of changes in all variables between groups were made by use of the repeated-measures ANOVA, and those of each measurement point were made using the Mann-Whitney *U* test. A 2-sided *P* value <.05 was considered significant.

Results

Women (n = 119) were approached for consent between February 1, 2011, and January 31, 2013. Of those approached, 24 women declined to participate, and 30 delivered beyond 32 weeks and were not eligible for participation. After randomization, 5 infants (3 assigned to the UCM group and 2 assigned to the ICC group) were excluded because of predefined criteria. Infants were excluded for the development of an acute abruption (n = 2) and cutting through the placenta (n = 2). There was also a single case of an infant being excluded because of instability as determined by the delivering OB. Two mothers gave consent, but their infants