# Umbilical Cord Milking Stabilizes Cerebral Oxygenation and Perfusion in Infants Born before 29 Weeks of Gestation

Takeshi Takami, MD, PhD[1], Yuusuke Suganami, MD, PhD[1], Daisuke Sunohara, MD, PhD[1], Atsushi Kondo, MD, PhD[1], Norio Mizukaki, MD[1], Tao Fujioka, MD[1], Akinori Hoshika, MD, PhD[1], Osamu Akutagawa, MD, PhD[2], and Keiichi Isaka, MD, PhD[2]

**Objective** To investigate the effects of umbilical cord milking at birth on cerebral perfusion and systemic perfusion in very low birth weight (VLBW) infants.

**Study design** Cerebral tissue oxygenation index and cerebral fractional tissue oxygen extraction were monitored in 50 stable VLBW infants (gestational age <29 weeks, birth weight <1250 g), with 26 allocated to the milked group and 24 to the control group. We used near-infrared spectroscopy 3-6, 12, 18, 24, 36, 48, and 72 hours after birth. Left ventricular end-diastolic dimension, left ventricular ejection fraction, left ventricle (LV) Tei index (measurement of left ventricular systolic and diastolic function), left ventricular cardiac output, and superior vena cava flow were measured concurrently using echocardiography.

**Results** There were no significant differences in gestational age and birth weight between the 2 groups. Hematocrit, left ventricular end-diastolic dimension, left ventricular cardiac output, and superior vena cava flow were higher in the milked group than in the control group, with improvement in the LV Tei index despite the absence of left ventricular ejection fraction changes within 24 hours after birth. Tissue oxygenation index increased and cerebral fractional tissue oxygen extraction decreased in the milked group within 24 hours after birth.

**Conclusion** Umbilical cord milking stabilized cerebral oxygenation and perfusion in VLBW infants by improving LV diastolic function by increasing LV preload. *(J Pediatr 2012;161:742-7)*.

Cerebral complications following very preterm birth are associated with long-term neurodevelopmental sequelae.[1] Hypotension and hypoperfusion of the brain have been related to cerebral damage in sick preterm infants during the immediate postnatal period.[2-4] Kluckow and Evans demonstrated that sick preterm infants who developed intraventricular hemorrhage (IVH) experienced a period of low superior vena cava (SVC) flow as a consistent marker of decreased upper body perfusion including cerebral blood flow within the first 48 hours of life.[5,6] Recently, we demonstrated that even stable extremely low birth weight infants have reduced cerebral oxygenation and perfusion immediately after birth, which likely result from low cardiac output attributable to decreased left ventricle (LV) contractility and increased peripheral vascular resistance.[7]

A study and Cochrane Review demonstrated that infants who had delayed cord clamping were less likely to require red blood cell transfusion for low blood pressure and had a lower incidence of IVH after birth.[8,9] Furthermore, Hosono et al showed in a recent randomized controlled study that umbilical cord milking facilitated the early stabilization of both blood pressure and urine output, and reduced the need for both red blood cell transfusion and circulatory and respiratory support in very low birth weight (VLBW) infants.[10,11] Cord milking had similar effects to delayed cord clamping in preterm infants in terms of initial hemoglobin values and the reduced need for red blood cell transfusions.[12] Red blood cell transfusion as therapy for anemia in preterm infants also improved cerebral oxygenation on near-infrared spectroscopy (NIRS).[13-17]

We hypothesized that umbilical cord milking may increase systemic blood volume, which will affect LV preload, left ventricular cardiac output (LVCO), and SVC flow as measured on echocardiography. Furthermore, milking may stabilize cerebral oxygenation and perfusion as indicated by cerebral tissue oxygenation index (TOI) and cerebral fractional tissue oxygen extraction (FTOE) measured with NIRS.

| | | | |
|---|---|---|---|
| FTOE | Fractional tissue oxygen extraction | MABP | Mean arterial blood pressure |
| Hct | Hematocrit | NIRS | Near-infrared spectroscopy |
| IVH | Intraventricular hemorrhage | $SpO_2$ | Oxygen saturation |
| LV | Left ventricle | SVC | Superior vena cava |
| LVDd | Left ventricular end-diastolic dimension | TOI | Tissue oxygenation index |
| LVCO | Left ventricular cardiac output | VLBW | Very low birth weight |

From the [1]Department of Pediatrics and [2]Department of Obstetrics and Gynecology, Tokyo Medical University, Tokyo, Japan

The authors declare no conflicts of interest.

0022-3476/$ - see front matter.  10.1016/j.jpeds.2012.03.053

## Methods

We evaluated 50 VLBW infants with a gestational age of <29 weeks and a birth weight of <1250 g, who were admitted to the neonatal intensive care unit of our institution between January 1, 2006 and December 31, 2009. Among the 50 subjects who were admitted after November 2007, 26 had umbilical cord milking, as milking management was introduced in our unit after November 1, 2007. However, as this procedure requires the presence of more than 3 doctors at birth, umbilical cord milking was not performed for every delivery. The subjects were divided into 2 groups: those who had umbilical cord milking (milked group, n = 26) or those who did not (control group, n = 24). All subjects were VLBW infants who (1) had no anomalies and who were not small for their gestational age (birth weight of <the 10th percentile for gestational age); (2) did not have severe electrolyte abnormalities or metabolic acidosis; and (3) were maintained in a stable respiratory condition with or without mechanical ventilation and had an oxygen saturation ($SpO_2$) level of >90% and a $PCO_2$ range of 30-50 mm Hg during the study period. Data from 12 of 16 extremely low birth weight infants in our previous study[7] were included in the controls (n = 24) for study. Infants who had cord milking were placed at or below the level of the placenta, and approximately 20 cm of the umbilical cord was vigorously milked towards the umbilicus 2 to 3 times before clamping the cord.[10] The milking rate was approximately 20 cm/s. The umbilical cord of the control group infants was clamped immediately after birth. The present study was approved by the Research Ethics Committee of our institution. Informed consent was obtained from all parents before conducting the study.

The oxygenated hemoglobin, deoxygenated hemoglobin, and total hemoglobin (= oxygenated hemoglobin + deoxygenated hemoglobin) levels and the TOI (oxygenated hemoglobin/total hemoglobin × 100) were measured using NIRS (NIRO-200/300; Hamamatsu Photonics KK, Shizuoka, Japan). The optode was placed in the frontotemporal region of the head with the sensors at 3-cm intervals.[18] Measurements were taken 3-6, 12, 18, 24, 36, 48, and 72 hours after birth, and each measurement session lasted for 30 minutes. The TOI was calculated as a median value of 450 measurements (15 minutes each) over the examination period. Cerebral FTOE was then calculated from the TOI and $SpO_2$ values as follows: $FTOE = (SpO_2 - TOI)/SpO_2$.[19]

Serial echocardiographic examinations were performed for all infants simultaneously with NIRS. All scans were performed by a single examiner (T.T.) [20] using the HP SONOS 2000 (Philips Healthcare, Bothell, Washington) ultrasound equipped with a 7.5-MHz transducer and a Philips iE33 (Philips Healthcare) ultrasound equipped with a 12.0-MHz transducer. The left ventricular end-diastolic dimension (LVDd) was measured as an index of LV preload. The end-systolic wall stress of the LV was measured as an index of LV afterload on M-mode echocardiography. Imaging was performed in the parasternal long-axis view according to the method of Colan et al.[21] Left ventricular ejection fraction was measured as an index of systolic function of the LV with M mode echocardiograms, taken in the parasternal long-axis view according to the method of Sahn et al.[22] Doppler measurements of the Tei index as an assessment of both the systolic and diastolic function of the LV were performed using the method proposed by Tei et al.[23] Doppler volumetric measurements of the LVCO and SVC flow were measured according to the methods of Alverson et al[24] and Kluckow et al,[5] respectively. The measurement of the echocardiographic variables was performed within 20 minutes.

Blood was collected from an arterial line or after heel lance. The hemoglobin value on admission was from the first blood sample collected after birth. Mean arterial blood pressure (MABP) was measured either directly or indirectly using an oscillometric technique with an inflatable cuff (BSN-2303; Nihon Kohden Corporation, Tokyo, Japan). $PCO_2$, hematocrit (Hct) values, and indirect MABP were measured after NIRS and echocardiographic measurement. Heart rate and $SpO_2$ in the right upper arm were continuously measured using pulse oximetry (Nellcor Pulse Oximeter N-200; Tyco Healthcare Japan, Tokyo, Japan). Heart rate, direct MABP, and $SpO_2$ were monitored and recorded concurrently with the NIRS measurements with a neonatal monitoring system (BSM-2300; Nihon Kohden Corporation). Median values were calculated over the measurement period.

Polycythemia was defined as a hemoglobin value of >22.0 g/dL on admission. Respiratory distress syndrome was defined on the basis of the clinical and radiographic findings and negative or weak microbubble test findings. Patent ductus arteriosus was considered as present in infants who were selected for indomethacin therapy for the following echocardiography findings: (1) a ductus arteriosus size of >2.0 mm; (2) a diastolic flow velocity of >3.0 m/s and at least one-third greater than the velocity of the systolic flow in the left pulmonary artery; and (3) a left atrium/aorta ratio of >1.5. IVH, as diagnosed by cranial ultrasound and graded from I-IV according to Papile's classification.[25] Necrotizing enterocolitis was defined as modified Bell's stage II or higher[26] and required radiologic evidence of pneumatosis, portal venous gas, or pneumoperitoneum in addition to the clinical and laboratory features of necrotizing enterocolitis. A diagnosis of periventricular leukomalacia was made if cysts were observed on cranial ultrasound or if magnetic resonance imaging showed multiple abnormalities, including cystic lesions, enlarged ventricles, delayed myelination, high-intensity areas in the white matter, and cortical atrophy.[27] The diagnosis of retinopathy of prematurity was based on the international classification criteria.[28]

Statistical analyses were performed using the computer package SPSS for Windows (SPSS Japan, Tokyo, Japan). Normally distributed continuous outcome variables were compared with the unpaired Student *t* test, and nonparametric