



Effects of Placental Transfusion on Neonatal and 18 Month Outcomes in Preterm Infants: A Randomized Controlled Trial

Judith S. Mercer, PhD, CNM^{1,2,3}, Debra A. Erickson-Owens, PhD, CNM^{1,2,3}, Betty R. Vohr, MD^{2,3}, Richard J. Tucker, BA³, Ashley B. Parker, BA³, William Oh, MD^{2,3}, and James F. Padbury, MD^{2,3}

Objective To assess the effect of delayed cord clamping (DCC) vs immediate cord clamping (ICC) on intraventricular hemorrhage (IVH), late onset sepsis (LOS), and 18-month motor outcomes in preterm infants.

Study design Women (n = 208) in labor with singleton fetuses (<32 weeks gestation) were randomized to either DCC (30-45 seconds) or ICC (<10 seconds). The primary outcomes were IVH, LOS, and motor outcomes at 18-22 months corrected age. Intention-to-treat was used for primary analyses.

Results Cord clamping time was 32 ± 16 (DCC) vs 6.6 ± 6 (ICC) seconds. Infants in the DCC and ICC groups weighed 1203 ± 352 and 1136 ± 350 g and mean gestational age was 28.3 ± 2 and 28.4 ± 2 weeks, respectively. There were no differences in rates of IVH or LOS between groups. At 18-22 months, DCC was protective against motor scores below 85 on the Bayley Scales of Infant Development, Third Edition (OR 0.32, 95% CI 0.10-0.90, P = .03). There were more women with preeclampsia in the ICC group (37% vs 22%, P = .02) and more women in the DCC group with premature rupture of membranes/preterm labor (54% vs 75%, P = .002). Preeclampsia halved the risk of IVH (OR 0.50, 95% CI 0.2-1.0) and premature rupture of membranes/preterm labor doubled the risk of IVH (OR 2.0, 95% CI 1.2-4.3).

Conclusions Although DCC did not alter the incidence of IVH or LOS in preterm infants, it improved motor function at 18-22 months corrected age. (*J Pediatr* 2016;168:50-5).

Clinical trial registration ClinicalTrials.gov: NCT00818220 and NCT01426698.

When cord clamping is delayed at birth or the cord is milked, infants receive a placental transfusion of 10-15 mL/kg during the first few minutes of life.¹ This additional blood improves hemodynamic stability and may reduce the risk of intraventricular hemorrhage (IVH)^{2,3} and the vulnerability of infants to inflammatory processes.⁴⁻⁶ This blood also contains stem cells that are important in repairing tissue and building immunocompetence.⁷ Recently, the American College of Obstetricians and Gynecologists recommended delayed cord clamping (DCC) for preterm infants when feasible, but the current obstetrical practice at birth remains immediate clamping.⁸⁻¹⁰

Prior studies on DCC in preterm infants have shown benefits without harm. The most recent meta-analysis by Rabe et al¹¹ on infants under 37 weeks found reduced rates of neonatal transfusion (OR 0.61, 95% CI 0.46-0.81, P < .0005), less IVH (OR 0.59, 95% CI 0.41-0.85, P < .005), and no difference in late onset sepsis (LOS). Backes et al¹² reported similar findings in infants less than 32 weeks adding a finding of lower mortality (OR 0.42, 95% CI 0.19-0.95, P = .04). Previously, we reported reduced rates of IVH and LOS¹³ and some protection of very low birth weight (VLBW) male infants against motor disability at 7 months corrected age.¹⁴

The current randomized controlled trial prospectively tested the effects of DCC for 30-45 seconds followed by 1 cord milking with the aim of confirming our prior work and providing long-term follow-up. Our a priori hypotheses were that DCC would reduce the incidence of IVH, LOS, and result in better motor function at 18-22 months.

Methods

This trial was conducted at Women and Infants' Hospital of Rhode Island with Women and Infants' Hospital and the University of Rhode Island Institutional Review Board approval. Thirty patients (14%) were enrolled prior to trial regis-

From the ¹University of Rhode Island, Kingston, RI; ²Alpert School of Medicine, Brown University; and ³Women and Infants Hospital of Rhode Island, Providence, RI

The main study was funded by the National Institute of Nursing Research (RO1 NR100015), and the 18-22 month follow-up was funded by the Thrasher Research Fund (9185). The authors declare no conflicts of interest.

Portions of the study were presented as an abstract at the meeting of the Pediatric Academic Societies, San Diego, CA, April 25-28, 2015, as well as an oral presentation at the Congress of Neonatal Societies, Budapest, Hungary, September 16-20, 2015.

0022-3476/\$ - see front matter. Copyright © 2016 Elsevier Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.jpeds.2015.09.068>

Bayley-III	Bayley Scales of Infant Development, Third Edition	LOS	Late onset sepsis
DCC	Delayed cord clamping	NICU	Neonatal intensive care unit
GA	Gestational age	PEC	Preeclampsia
GM	Germinal matrix	PROM	Premature rupture of membranes
ICC	Immediate cord clamping	PTL	Preterm labor
IVH	Intraventricular hemorrhage	VLBW	Very low birth weight

tration, but no data were examined prior to trial registration. An independent data safety and monitoring committee reviewed the data after 36, 100, and 150 infants were randomly assigned and identified no concerns. Women with a singleton pregnancy estimated at 24-31.6 weeks gestation by obstetrical evaluation were eligible irrespective of mode of delivery. Exclusion criteria included multiple gestation, prenatally diagnosed major congenital anomalies, severe or multiple maternal illnesses, and mothers who were at risk for loss to follow-up. Blocked stratified randomization of subjects born before or after 28 weeks to the immediate cord clamping (ICC) or DCC group was used to assign the groups with a prespecified equal probability. Sequenced and sealed envelopes identifying the stratification and group assignment on cards were prepared by a statistician not involved in the trial and kept in a locked file box in the labor and delivery unit. All participants were screened, consented, and enrolled by study nurses following written informed consent. Study nurses randomized mothers based on the next study card designation when women went into active labor.

Women were randomized to either DCC followed by 1 milking of the cord (intervention group) or ICC (control group). For all births, research personnel used a stopwatch to record the exact timing of cord clamping. Once the cord was cut, the infant was moved to the warmer and placed on a warming mattress. All subsequent care was managed by the neonatal team in attendance. For the DCC group, the obstetrician placed the infant in a sterile warm towel or blanket and held the infant approximately 10-15 inches below the mother's introitus at vaginal delivery or below the level of the placenta at cesarean delivery. Care was taken to avoid traction on the cord. Suctioning was at the discretion of the obstetrician. The research nurse, using a stopwatch, counted out the time elapsed in 10-second intervals to the obstetrician. At 30-45 seconds, the obstetrician was asked to milk the infant's cord once, then clamp and cut the umbilical cord. If unable to carry out the DCC protocol as planned, the cord was milked quickly 2-3 times before clamping when possible ($n = 11$). In the event that the timing of the cord clamping was less than 30 seconds with no cord milking and the baby was randomized to the DCC group, a protocol violation report was completed and the infant remained in the DCC group for primary intention-to-treat analyses ($n = 15$). The ICC group received routine care of cord clamping in less than 10 seconds. Cranial ultrasounds were obtained at 1, 7, and 28 days. Formal developmental follow-up assessments at 7 and 18-22 months corrected age were completed.

IVH was defined as bleeding in the brain assessed by cranial ultrasound readings using the criteria of Papile.¹⁵ The staff pediatric radiologist read the ultrasound initially followed by a collaborating pediatric radiologist masked to the infants' grouping. Discrepancies were adjudicated by consensus through discussion among radiologists. LOS was defined as a positive bacterial blood culture after 72 hours of age. The Bayley Scales of Infant Development, Third Edition (Bayley-III) was used to assess cognitive, language, and

motor function.¹⁶ The motor composite score and subscores for fine motor and gross motor skills were analyzed. The Bayley-III composite score has a mean \pm SD of 100 ± 15 .

Secondary outcome variables included safety variables (Apgar scores, initial temperature upon admission, peak bilirubin in the first week of life), initial blood pressure, initial hematocrit, necrotizing enterocolitis, bronchopulmonary dysplasia, and retinopathy of prematurity as diagnosed by attending clinicians. Necrotizing enterocolitis was diagnosed based on Bell criteria, bronchopulmonary dysplasia was defined as requiring oxygen therapy at 36 weeks postmenstrual age or death, and retinopathy of prematurity was identified by an ophthalmologist per routine eye examinations.

The study could not be blinded because of the obvious nature of the intervention. Our institutional policy requires the presence of a neonatology staff member at delivery because of early gestation. Staff who attended each birth were asked not to reveal the infant's grouping in the infant's medical records. Personnel collecting on-going clinical data and the follow-up staff completing the developmental assessment remained blinded.

The power analysis was based on our phase 1 study¹³ and expected treatment effects for a simple test of proportions of group differences (ICC vs DCC) for the primary study outcome of IVH. We conservatively estimated an OR of about 2.5 for this new study, which yielded a sample size of 92 per group for power of 0.80. Given the need for follow-up, we allowed for an attrition rate of about 15%, resulting in a total baseline sample size of 212 VLBW infants. The use of block-stratified randomization enhanced the study design sensitivity.

The diagnoses of preterm labor (PTL) and premature rupture of membranes (PROM) were not discrete among the subjects. Consequently, we combined them into 1 variable PROM/PTL that represented women who had either diagnoses. Both conditions can be associated with intrauterine inflammation.¹⁷

Data analyses included Pearson χ^2 tests, t tests, Wilcoxon rank-sum tests for non-normally distributed variables, and multiple logistic and linear regression models to adjust for possible confounders. No correction was used to adjust for multiple tests. For outcomes, ORs were calculated along with appropriate 95% CIs. Primary analyses were conducted using intention-to-treat. Post-hoc sensitivity analyses using actual treatment were indicated and performed to assess the robustness of the findings.¹⁸

Results

Pregnant women ($n = 211$) between 24 and 31.6 weeks gestation were randomized from May 15, 2008, through January 30, 2012 (Figure 1; available at www.jpeds.com). There were 107 infants in the ICC and 104 in the DCC group. Three infants were withdrawn (congenital anomalies and birth injury that precluded randomization), leaving a total sample of 208 mother-infants dyads. Maternal and infant

Download English Version:

<https://daneshyari.com/en/article/6219849>

Download Persian Version:

<https://daneshyari.com/article/6219849>

[Daneshyari.com](https://daneshyari.com)