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Effects of Delayed Cord Clamping in Very Low Birth Weight Infants

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Abstract

Background—Delayed cord clamping may be beneficial in very preterm and low birth weight infants.

Study Design—A randomized unmasked controlled trial

Setting—The study was performed in three centers of the NICHD Neonatal Research Network

Hypothesis—Delayed cord clamping in very preterm and very low birth weight infants will result in an increase in hematocrit at 4 hours of age.

Methods—Infants with a gestational age of 24–28 weeks were randomized into early (< 10 seconds) or delayed (30–45 seconds) cord clamping. The primary outcome was venous hematocrit at 4 hours of age. Secondary outcomes included delivery room management, selected neonatal morbidities and the need for blood transfusion during the infants' hospital stay.

Results—Thirty three infants were randomized: 17 to the immediate cord clamping (ICC, cord clamped at 7.9 ± 5.2 seconds, $m \pm SD$) and 16 to the delayed cord clamping (DCC, cord clamped at 35.2 ± 10.1 seconds) group. The hematocrit was higher in the DCC group (45 ± 8 versus $40 \pm 5\%$, $p < 0.05$). The frequency of events during delivery room resuscitation was almost identical between the two groups. There was no difference in hourly mean arterial blood pressure during the first 12 hours of life, there was a trend in the difference in the incidence of selected neonatal morbidities, hematocrit at 2, 4 and 6 weeks as well as the need for transfusion, but none of the differences was statistically significant

Conclusion—A higher hematocrit is achieved by delayed cord clamping in very low birth weight infants suggesting effective placental transfusion.

Background

Autologous transfusion of blood to the newborn as a result of delayed cord clamping at birth is a well-described phenomenon in term infants resulting in higher hematocrit and blood

volume (1-5) as well as physiologic changes in gastro-intestinal, Cardio-pulmonary (6-8) and renal functions. (9) In preterm low birth weight infants, placental transfusion results in lower incidence of respiratory distress syndrome (10), higher blood volumes and hematocrit, and fewer infants with hypotension (11) It is noted that the participants in these studies were larger and of higher gestational age because the survival rate of very low birth weight infants in that period was low. More recent studies involving very preterm and very low birth weight infants documented a higher hematocrit and red cell volume (12-14), lower incidence of intraventricular hemorrhage and late onset sepsis (15). In two systematic reviews, Rabe et al concluded that delayed cord clamping in very low birth weight infants may be beneficial and appears to be safe (16,17). Despite these positive observations, immediate cord clamping is still the standard practice among obstetricians

We conducted this clinical trial to gather additional evidence for efficacy of delayed cord clamping in providing additional blood volume in very preterm, very low birth weight infants.

Methods

This study was approved by the Institutional Review Board of the three participating centers of the Neonatal Research Network (University of Alabama, Birmingham, Alabama, Rainbow Babies and Children's Hospital, Cleveland, Ohio and Women and Infants Hospital, Providence RI) Women with gestational age between 24 0/7 and 27 6/7 weeks singleton pregnancies, who were admitted for preterm labor were eligible for the study. With approval from the attending obstetricians, informed consent was obtained from the parent. The subject was randomized (per phone call to the RTI International Data Coordinating Center) into one of two groups: immediate cord clamping (ICC), where the umbilical cord was clamped < 10 seconds after delivery of the infant's presenting part, and Delayed cord clamping (DCC), where the infant's umbilical cord was clamped at 30-45 seconds after delivery of the infant's presenting part. Randomization was stratified by mode of delivery and center. At delivery, research personnel were present to time the delivery and the clamping of the umbilical cord with a stop watch. The infant was kept at approximately 10 cm below the birth canal (or abdomen in the case of cesarean section). The management of the infants at birth and the subsequent course in the intensive care nursery was at the discretion of the attending clinicians. The study was not blinded, although efforts were made to avoid revelation of the grouping of the infants to the attending clinicians. The primary outcome was venous hematocrit obtained at 4 hours of age. Secondary outcomes included: delivery room management and hourly mean arterial blood pressures measured during the first 12 hours, either by transducer connected to the umbilical artery or by Dynamap® in the absence of the umbilical arterial lines. Other variables obtained during the course of infants' stay in the nursery included: capillary hematocrit at 2, 4 and 6 weeks of age, amount of blood withdrawn for clinical indications and amount of blood transfused. The neonatal morbidities recorded were intraventricular hemorrhage by cranial ultrasound as classified by Papile et al (18), culture proven late onset sepsis (Sepsis occurring > 3 days of age), necrotizing enterocolitis (NEC) > stage 2 per Bell's classification (19), bronchopulmonary dysplasia defined as oxygen treatment at 36 week post menstrual age, and retinopathy of prematurity (all grades).

Statistical analysis

We performed statistical analysis using Fisher's exact test for categorical data and student's t test on continuous co-variates. All values are expressed as mean \pm SD. A p value <0.05 was considered statistically significant.

Sample size calculation was based on venous hematocrit in ICC group of infants at 4 hours of age ($46 \pm 4\%$ SD) (5). Assuming a 10% relative increase of hematocrit by delayed cord clamping, and 90% power, the calculated sample size was 16 infants in each group. Analyses were performed at the Research Triangle Institute (RTI International NC), using SAS software.

Results

The trial was conducted between May 2000 and June 2001. During this period of time, 190 mothers were screened, 97 were eligible, and 54 (56%) consented to the study. Of these, 33 (61%) were randomized (17 ICC and 16 DCC). The majority of those mothers who consented to the study but were not randomized were due to logistic reasons (research personnel not available when delivery took place ($n=14$) and delivery beyond 28 weeks ($n=7$). The umbilical cords were clamped at 7.9 ± 5.2 seconds in the ICC group vs. 35.2 ± 10.1 seconds ($p < .001$) in the DCC group.

There was no difference in maternal and infant demographic and clinical characteristics between the two groups (Table 1 and 2). The procedures performed during delivery room management of the study infants and their Apgar score at 1 and 5 minutes were almost identical between the 2 groups (Table 3). The hourly mean arterial blood pressure ranged between 26 to 32 mmHg during the first 12 hours and no difference was observed between the 2 groups. The venous hematocrit values were higher in the DCC group (44.9 ± 7.8 vs. 40.2 ± 5.1 (SD, $p < 0.05$). At 2, 4, and 6 weeks of age and at the time of discharge, the hematocrit values were still higher in the DCC group but the differences were not statistically significant (Table 4). There were no differences in neonatal morbidities between the two groups (Table 5). The amounts of blood withdrawn for diagnostic reasons was similar between the two groups and the amount transfused during the infants' hospital stay were higher among the ICC group vs. the DCC group but statistically not significant (Table 6).

Discussion

Our findings of a higher venous hematocrit values at 4 hours of age in the delayed cord clamping group indicates an effective placental transfusion at the time of birth when cord clamping is delayed. The finding is consistent with previous studies (12-14). Although our sample size is small, the almost identical findings of various delivery room events suggest that the procedure of delayed cord clamping for a mean duration of 35 seconds is feasible and safe in this population. This is an important observation since many obstetricians are concerned that delaying the clamping of the cord may compromise the welfare of an infant during delivery.

We demonstrated that delayed cord clamping in this high risk population resulted in a trend toward a higher hematocrit values during the first 6 weeks, less need for transfusion during hospital stay and lower incidence of late onset sepsis and necrotizing enterocolitis (beneficial effects) as well as a higher incidence of intraventricular hemorrhage and retinopathy of prematurity (adverse effects). However, these beneficial and adverse outcomes of the intervention were all collected as secondary variables and were not powered for statistical significance in our sample size calculation. With reference to the higher hematocrit level at 6 weeks of age, Ultee et al recently showed that DCC is associated with a higher hematocrit levels in late preterm infants at 10 weeks of age when compared with those with ICC (20). In a retrospective meta-analysis Rabe et al (17) reviewed infants born below 37 weeks gestation and enrolled into a randomized study of delayed cord clamping (30 seconds or more) versus immediate cord clamping (less than 20 seconds) after birth. Systematic search and analysis of the data were done according to the methodology of the

Cochrane collaboration. They analyzed the results of 10 studies describing a total of 454 preterm infants which met the inclusion and assessment criteria. Major benefits of the intervention were higher circulating blood volume during the first 24 h of life, less need for blood transfusions ($p=0.004$) and less incidence of intraventricular hemorrhage ($p=0.002$). Recent studies have shown a lower incidence of late onset sepsis and intraventricular hemorrhage with delayed cord clamping (15) based on the rationale that effective placental transfusion provided additional amount of stem cells that may confer additional immunologic competence (21,22) for the former observation and additional blood volume that provides circulatory stability for the latter.

More recently, Hosono and coworkers introduced a novel method of ‘umbilical cord milking in lieu of delayed cord clamping to achieve placental transfusion for very preterm infants. The demonstrated that such procedure resulted in a higher blood pressure and urine outputs during the first 12 hours of life (23), shorter duration of assisted ventilation and less need for blood transfusion. (24) Moreover, since it was known that umbilical cord blood contains various valuable stem cells such as haematopoietic stem cells, endothelial cell precursors, mesenchymal progenitors and multipotent/pluripotent lineage stem cells, the merit of delayed cord clamping has been magnified (25)

It appears that in very preterm infants, placental transfusion achieved by delayed cord clamping or umbilical cord milking is a relatively inexpensive and safe intervention that could provide significant benefits. A single center large (sample size = 220) randomized controlled trial to test the hypothesis that delayed cord clamping will result in lower incidence of intraventricular hemorrhage and late onset sepsis is currently in progress at Women and Infants’ Hospital of RI (Judith Mercer, PhD, personal communication). Confirmation of the safety and benefits of delayed cord clamping by this clinical trial will provide an impetus to alter our practice of cord clamping during delivery of these high risk infants.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. W. Kenneth Poole (DCC Principal Investigator) and Scott McDonald (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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NRN Steering Committee Chair: Alan Jobe, MD PhD, University of Cincinnati.

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Table 1

Maternal demographic and clinical characteristics

	ICC (n=17)	DCC (n=16)
Age (years)	25 ± 8 (SD)	27 ± 9
Gravida 1	41	38
2	35	38
>2	24	25
Race White	12	38
Black	53	50
Hispanic	29	13
Other	6	0
Hypertension	18	6
PIH	29	13
Prolong ruptured membrane	24	31
Oligohydramnios	12	13
Fetal distress	29	13

All values except for age are in %. All p values were >0.05

Table 2

Infants characteristics

	ICC (n=17)	DCC (n=16)
Birth Weight (gm)	767 ± 243 (SD)	854 ± 222
Gestation (wks)	26 ± 1.1	26 ± 1.4
Gender (% male)	41	44
SGA (n)	3	0

Table 3

Delivery room management

Parameter	ICC (n=17)	DCC (n=16)
O ₂ administered	17/17	16/16
Bagging and mask	10/17	11/16
Intubated	10/17	9/16
Apgar score 1 min Median (Range)	4.9 (2.7) 6 (1-8)	4.1 (2.7) 4.5 (0-8)
Apgar scores at 5 min Median (Range)	6.6 (1.5) 7 (3-9)	6.4 (2.0) 7 (1-9)

All p values were n.s.

Table 4

Hematocrit values (% , m+SD) of study infants

Age	ICC (n=17)	DCC (n=16)
4 hours	40.2 ± 5.1	44.9 ± 7.8 *
2 weeks	37.7 ± 3.7	39.4 ± 5.0
4 weeks	35.4 ± 5.1	36.2 ± 5.4
6 weeks	34.6 ± 6.2	37.1 ± 7.0
Before discharge	31.0 ± 8.8	33.8 ± 7.7

All p values were n.s.

Table 5

Selected neonatal morbidities (%) in study infants

Morbidity	ICC N=17	DCC N=16	RR (CI) ICC vs DCC
Late onset sepsis	8/17 (47%)	5/16 (31%)	1.51 (0.62 – 3.65)
Necrotizing enterocolitis	4/17 (24%)	2/16 (13%)	1.88 (0.40 – 8.90)
Intraventricular hemorrhage	3/17 (18%)	4/16 (25%)	0.71 (0.19 – 2.67)
Retinopathy of prematurity	5/15 (33%)	6/12 (50%)	0.67 (0.27 – 1.66)
Patent ductus arteriosus	5/17 (29%)	7/16 (44%)	0.67 (0.27 – 1.69)

Table 6

Amount of blood withdrawn and transfused (mL/kg) during the hospital stay

Measure	ICC n=17	DCC n=16
Blood withdrawn	36 ± 21	33 ± 23
Blood transfused	160 ± 157	128 ± 159

Mean ± SD p value n.s.