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ORIGINAL ARTICLE

Seven-month developmental outcomes of very low birth weight infants enrolled in a randomized controlled trial of delayed versus immediate cord clamping

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Objective: The results from our previous trial revealed that infants with delayed cord clamping (DCC) had significantly lesser intraventricular hemorrhage (IVH) and late-onset sepsis (LOS) than infants with immediate cord clamping (ICC). *A priori*, we hypothesized that infants with DCC would have better motor function by 7 months corrected age.

Study Design: Infants between 24 and 31 weeks were randomized to ICC or DCC and follow-up evaluation was completed at 7 months corrected age.

Result: We found no differences in the Bayley Scales of Infant Development (BSID) scores between the DCC and ICC groups. However, a regression model of effects of DCC on motor scores controlling for gestational age, IVH, bronchopulmonary dysplasia, sepsis and male gender suggested higher motor scores of male infants with DCC.

Conclusion: DCC at birth seems to be protective of very low birth weight male infants against motor disability at 7 months corrected age. *Journal of Perinatology* (2010) **30,** 11–16; doi:10.1038/jp.2009.170; published online 22 October 2009

Keywords: cord clamping; motor outcomes; very low birth weight infants; randomized controlled trial; gender

Introduction

A brief delay in cord clamping at birth results in approximately 10 to 15 ml kg^{-1} of additional whole cord blood for the very low birth weight (VLBW) infant[1] without placing the infant at increased risk.[2–3] Aladangady *et al.*[1] found that infants with delayed cord clamping (DCC) obtained variable amounts of additional blood with a mean of 12 ml kg^{-1} from a 30 to 90 s delay and lowering of the infant at vaginal and cesarean birth. Several beneficial effects of DCC have been demonstrated for preterm infants.[1,4–13] In a meta-analysis of randomized controlled trials on DCC in preterm infants, Rabe *et al.*[2–3] found a decreased need for transfusion and lower rates of intraventricular hemorrhage (IVH) with no evidence of adverse effects. Our randomized controlled trial[14] also showed that infants in the DCC group had significantly lesser IVH and late-onset sepsis (LOS) with an advantage for male infants for both outcomes. IVH, sepsis and male sex have all been reported to be associated with adverse neurodevelopmental outcomes among preterm infants.[15] *A priori*, we hypothesized that VLBW infants with DCC would have better motor function by 7 months corrected age when compared with VLBW infants with immediate cord clamping (ICC). The hypothesis was based on the concept that infants with DCC have more red blood cell flow to the brain (motor cortex) thus better oxygen delivery in the initial few days of life[16] and that DCC is associated with decreased rates of neonatal morbidities.[3] Also, the lower incidence of IVH and sepsis may be reflected in better motor performance at 7 months. No prior cord clamping studies have reported neurodevelopmental outcomes after discharge from the neonatal intensive care unit. The male advantage with reference to IVH and LOS with DCC also prompted examination of gender differences in neurodevelopmental outcomes.

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Methods

Patient population

The study cohort was derived from the 72 infants in the Delayed Cord Clamping Trial.[14] The study was conducted at Women and Infants' Hospital, Providence, RI, with infants born between August 2004 and December 2005. The institutional review boards from Women and Infants' Hospital and the University of Rhode Island granted approval of the study. Informed consent, which included post-discharge follow-up, was obtained from all subjects before randomization.

Protocol at birth

The neonatal protocols have been fully described.[14] Briefly, mothers between 24 and 31.6 weeks gestation consented for their infants

and were assigned by block stratified (24 to 27 weeks, 28 to 31 weeks) randomization through numbered cards in opaque envelopes to receive either ICC or DCC. Research nurses enrolled the mothers and attended the births to assign randomization. The obstetrician either clamped the umbilical cord immediately after birth (<10 s, usual practice), or the cord was clamped at 30 to 45 s and the infant was held in a sterile blanket approximately 10 to 15 inches below the placenta. The subsequent clinical management of the infant was at the discretion of the attending neonatologist.

Neurodevelopmental assessments at 7 months

At the median age of 7 months corrected age, the survivors were seen at our Follow-Up Clinic. Bayley Scales of Infant Development-II (BSID-II) mental and motor scales[17] were administered to the study infants by trained certified psychologists whose inter-rater reliability was 0.90. This was followed by a medical history and physical examination completed by a physician or nurse practitioner. The staff was masked to the assigned study groups. BSID-II scores of 100 ($\pm$15) represent the mean and $\pm$1 s.d. A score below 70 is 2 s.ds. below the mean.

Statistical methods

Two-sample *t*-tests and χ^2 analyses were used to test for differences between the groups on demographics, historical and physical findings, and motor function at 7 months corrected age. Correlations were conducted to determine which variables were most strongly associated with an infant's motor scores and to identify potentially confounding variables. A multiple linear regression model for main effects was used to account for the effect of late cord clamping while controlling for potentially confounding variables. An Interaction Term Model was used because of the strength of gender in the regression model. Statistical analyses were performed using SAS software (SAS Institute, Cary, NC, USA). All reported *P*-values are two-tailed.

Results

Five children died before the 7-month visit and 58 (87%) of the 67 survivors at 7 months corrected age were seen (Figure 1). This included 29 (88%) of the infants in the ICC group and 29 (85%) in the DCC group. Nine children were either lost to follow-up or did not have a complete BSID−II administered for health, transportation or behavioral reasons. The infants lost to follow-up were older at birth (30 vs 28 weeks, $P=0.008$), larger (1352 vs 1158 g, $P=0.14$), had fewer days of oxygen use (15 vs 32 days, $P=0.28$) and shorter lengths of stay (55 vs 67 days, $P=0.33$) than infants evaluated.

Tables 1 and 2 show the maternal and child characteristics. There were no significant differences in demographic and perinatal characteristics between the ICC group and the DCC group.

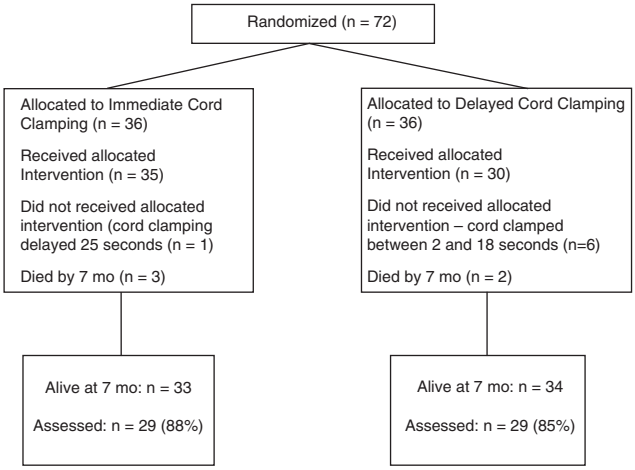

Figure 1 Flow chart of children included in the Cord Clamping Study and 7 month follow-up.

Table 1 Infant and maternal demographic characteristics

Variables	*ICC (n = 29)*	*DCC (n = 29)*	P-*value*
Birth weight[a]	1138 ± 373	1178 ± 364	0.68
Gestational age at birth	28.1 ± 2.28	28.1 ± 2.14	0.91
Gender, % male	15 (52%)	18 (62%)	0.43
Race			
White	17 (59%)	12 (41%)	0.53
Hispanic	9 (31%)	10 (35%)	
Black	2 (7%)	5 (17%)	
Other	1 (3%)	2 (7%)	
Maternal education less than high school	6	8	0.54
Maternal education, years	13	13.3	0.71
English spoken in the home	29 (100%)	25 (86%)	0.12
Corrected age at assessment (months)	8.4 ± 3.1	8.9 ± 3.1	0.57
Range	(6 to 18.6)	(6.3 to 18.3)	
Median	7.3	7.3	

Abbreviations: DDC, delayed cord clamping; ICC, immediate cord clamping.
[a]Mean+s.d.; *n* (%) unless otherwise noted.

Note that the median corrected age of assessment was 7.3 months in both groups.

The BSID-II Mental Developmental Index and Psychomotor Developmental Index (PDI) scores at approximately 7 months corrected age were similar for the infants in the ICC group and the DCC group (Table 3). There were no group differences in weight, length or head circumference equal to or less than the 10th percentile, post-discharge emergency room visits, hospitalizations or use of medications or early intervention participation (data not

Table 2 Perinatal characteristics of study subjects

Variables	*ICC (n = 29)*	*DCC (n = 29)*	P-*value*
Apgar at 5 min, median	8	8	0.88
IVH, all grades[a]	10 (34%)	5[a] (17%)	0.13
Late-onset sepsis[b]	6 (21%)	1[a] (3%)	0.10
Suspected NEC	16 (55%)	11 (38%)	0.19
NEC	1 (3%)	1 (3%)	1.0
BPD	6 (21%)	6 (21%)	1.0
Percent of BW <10th percentile	1	1	0.98

Abbreviations: BW, body weight; BPD, bronchopulmonary dysplasia; DDC, delayed cord clamping; IVH, intraventricular hemorrhage; ICC, immediate cord clamping; NEC, necrotizing enterocolitis.
[a]*n* (%).
[b]One child had ICC (protocol violation).

Table 3 Bayley Scales of Infant Development motor and mental outcomes at 7 months corrected age of preterm infants born 24 to 31.6 weeks

Variables	*ICC (n = 29)*	*DCC (n = 29)*	P-*value*
PDI (mean+s.d.)[a]	84 ± 16	84 ± 19	0.98
PDI[b]			
⩾85	15 (52%)	19 (66%)	0.15
70–84	9 (31%)	3 (10%)	
<70	5 (17%)	7 (24%)	
MDI (mean+s.d.) [a]	88 ± 11	84 ± 16	0.19
MDI[b]	*(n = 28)*		
⩾85	22 (79%)	20 (69%)	0.51
70–84	4 (14%)	4 (14%)	
<70	2 (7%)	5 (17%)	
PDI+s.d. (n)[b]			
Males	81 ± 13 (*n* = 15)	86 ± 13 (*n* = 18)	0.11
Females	87 ± 18 (*n* = 14)	78 ± 18 (*n* = 10)	
MDI+s.d. (n)[b]			
Males	85 ± 12 (*n* = 14)	86 ± 13 (*n* = 18)	0.11
Females	92 ± 8 (*n* = 14)	78 ± 19 (*n* = 10)	

Abbreviations: ICC, immediate cord clamping; DCC, delayed cord clamping; one infant had PDI assessment but was unable to complete MDI assessment due to irritability. One female infant in the DCC group with MDI <70 was a protocol violation and another developed a devastating syndrome unrelated to birth.
[a]*t*-test.
[b]χ^2-test.

shown). Repeating the analyses by actual treatment group rather than by intention-to-treat group did not change the significance of any of the outcomes.

Additional *t*-tests were used to explore relationships between the PDI and the categorical variables. The infants who had an oxygen requirement at 36 weeks (bronchopulmonary dysplasia) had lower PDI scores (72 vs 88, $P<0.01$) compared with infants without oxygen use. Infants with confirmed sepsis also scored lower on the PDI (66 vs 87, $P<0.01$) than those with no sepsis. There was no significant difference in PDI scores between the infants with or without IVH (80 vs 86, not significant). There were no differences in the PDI scores of infants with ICC versus DCC (84 vs 85, not significant) or for males and females (85.6 vs 82.7, not significant).

A Main Effects Regression Model (see Table 4) was used to predict the PDI as a continuous variable for VLBW infants with ICC or DCC, controlling for gestational age, male sex, IVH, oxygen use at 36 weeks and sepsis. (None of the variables used for socioeconomic status—maternal age, education, marital status, type of insurance—were correlated with either DCC or PDI or any of the predictor variables and were not included.) These predictor variables explained 29% of the variance in the PDI scores ($P = 0.007$). The model indicates that LOS and oxygen use at 36 weeks significantly lowered motor scores by 19 and 13 points, respectively, when the other variables are held constant.

Table 4 Regression analysis of predictors of motor outcomes (PDI scores) at 7 months corrected age

Predictor variables	*Main Effects Model*		*Interaction Term Model*	
	b	P-*value*	b	P-*value*
Gestational age	−0.66	0.56	−0.7	0.51
IVH	0.52	0.88	3.5	0.51
BPD	−12.71*	0.01	−17.5**	0.006
Sepsis	−18.9**	0.007	−16.6*	0.01
Late clamp	−3.9		−13.8*	0.01
Male	8.33	0.06	−0.2	0.96
Male × late clamp	—		18.3*	0.04
R^2	29%**	0.007	35%**	0.005

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, Intraventricular hemorrhage.
b: unstandardized regression coefficient; *$P<0.05$; **$P<0.01$.
In the Main Effects Model, the second column, 'b' (regression coefficient) represents the effect of the predictor variable on the dependent variable, PDI, taking into account each level of the the other predictor variables. Thus, 'b' represents the number of units that the PDI scores would be expected to change, given the condition listed in the first column, while holding the values for all the other variables constant. For example, if an infant had sepsis, one could expect that the PDI score for that infant would be 18.9 points less than if he did not have sepsis. Being male raised the score by 8 points suggesting the need for an interaction term.
In the Interaction Term Model in the third column, 'b' for the interaction term (male × late clamping) is 18.3 points indicating that if an infant was male and had late clamping, his score on the PDI would be 18 points higher than if he had early clamping. In the presence of an interaction term in the model, the coefficients for the lower-order terms (male, late clamped alone) no longer represent main effects on PDI and are not independent of the other variables in the model. They represent the effects of male when not late clamped, and the effects of late clamp when not male.

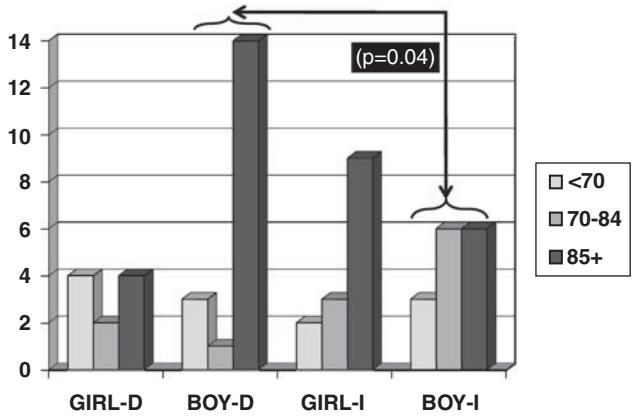

Figure 2 Number of girls and boys in each Psychomotor Developmental Index Score Range with delayed (D) or immediate (I) cord clamping at 7 months corrected age. The difference between the boys with immediate cord clamping and delayed cord clamping is significant ($P = 0.04$). No difference was noted between the girls ($P = 0.33$).

Male gender appeared to influence the model as it trended toward significance ($P = 0.06$).

Owing to the strength of the variable male in our Main Effects Model and our previous finding that DCC appeared to be more protective for males with lower rates of IVH and LOS, an interaction term was created between male gender and DCC (Table 4). In this model, the regression coefficient for the product term, male × late clamped, indicates that male infants who had DCC had PDI scores 18 points higher compared with females or infants with ICC when controlling for the other variables. The coefficient of multiple determination, R^2, is 35% for the Interaction Model ($P \leqslant 0.005$).

Figure 2 shows distribution of infants by gender who fell into PDI ranges of <70, 70 to 84 and 85 points or greater. Differences between male infants with ICC versus DCC reached significance.

Discussion

This is the first report of developmental outcomes of VLBW infants after a cord clamping intervention. No significant differences in Bayley scores were identified using bivariate statistical methods between the infants in the ICC and DCC groups at 7 months corrected age. However, using regression analyses to control for potential confounding factors, a brief delay (30 to 45 s) in cord clamping with the infant held below the level of the placenta was found to be associated with higher Bayley PDI scores for VLBW male infants at 7 months corrected age. Male infants with DCC had motor scores more than 1 s.d. higher than males with ICC when controlling for neonatal intensive care unit morbidities.

Being born preterm places an infant at greater risk for both cognitive and motor delay. Approximately 30 to 40% of VLBW infants experience some delay in motor functioning sometime during childhood.[18] The exact mechanisms contributing to motor delay are unknown, although data suggest that physiologic stressors associated with premature birth can disrupt regionally specific brain maturation.[19] Motor compromise is more common among VLBW infants with brain injury.[20] Damage occurring in the motor portions of the cortex, corpus callosum and basal ganglia seems to cause children to have a predisposition for motor disturbances.[19] We speculate that hypovolemia, secondary to ICC, may be disruptive to the developing brain resulting in subsequent motor delay. One mechanism may be that having less blood volume may contribute to cardiovascular instability resulting in the loss of autoregulation within the brain. Poor perfusion can lead to ischemic damage by reducing oxygen delivery to the motor cortex in the first few days of life. Hypovolemia immediately after birth, however, is extremely difficult to diagnose, measure or confirm. Alternatively, our findings of lower PDI scores in the ICC group may be related to the higher incidence of IVH and LOS. Both of these conditions have been found to be associated with developmental delay.[15]

VLBW infants are at greater risk than term infants for hypovolemia when the cord is immediately clamped at birth. Proportionately more of preterm infants' fetal-placental blood volume is in the placenta.[21] Generally, DCC results in more blood and red cell volume at birth.[1] At birth, the cardiac output to the lung must increase from the 8% level in fetal life to the 45% needed for neonatal life and adult circulation. Therefore, some of the blood from the fetal 'lung', the placenta, is needed by the neonatal lung for adequate expansion and recruitment of lung tissue. When there is little opportunity for placental transfusion, the infant is left with only the blood that was in the body at the time of cord clamping. Placental transfusion creates an increase in the circulatory bed at the same time that the infant's organs (lung, liver, kidney and so on) begin to assume the functions sustained by the placenta during fetal life.

Data to support this hypothesis are limited in part due to the lack of a simple straightforward tool for blood volume measurement. Aladangady *et al.*[1] reported that DCC resulted in approximately 12 ml kg^{-1} more blood volume in preterm infants. Nelle *et al.*[5] reported improved systemic and cerebral hemoglobin transport in preterm infants (<1500 g) after a 30 s delay in cord clamping while lowering the infant below the placenta. Higher blood and red cell volume may offer protection against hypovolemia and the resulting loss of autoregulation and ischemic damage.

Children in this study who had bronchopulmonary dysplasia had significantly lower Bayley Motor Scores consistent with the findings of others.[15] Our research supports earlier studies[19,22] showing that preterm children with chronic lung disease score lower in motor ability when assessed at 18 to 22 months (We could find no reported results at 7 months). Two studies followed large samples of preterm infants with bronchopulmonary dysplasia who were born between 1989 and 1991 when surfactant and postnatal

steroid use was standard practice. Motor function was delayed at all ages and bronchopulmonary dysplasia predicted poorer motor outcome at ages 2.5 to 3 years after controlling for other risks of age, gender, race and socioeconomic status.[23–24]

Previously we reported that children in our study who had DCC had less LOS, especially male infants (owing to smaller sample size, LOS does not reach significance in this analysis). Our data suggest that ICC may increase the risk of LOS particularly in male VLBW infants. We found that children who had LOS while in the neonatal intensive care unit also had significantly lower motor scores at 7 months corrected age. Stoll *et al.*[25] found more developmental delays in infants with LOS. At 18 to 22 months follow-up, infants with confirmed sepsis were more likely to have a lower BSID-II score, more cerebral palsy and more vision impairment than infants without sepsis.[25]

DCC was associated with protection of male infants against IVH and sepsis in the neonatal intensive care unit and improved motor outcomes at 7 months corrected age.[14] Preterm male infants are known to have higher neonatal mortality and more long-term impairment when compared with preterm female infants.[26] Hintz *et al.*[27] reported neurodevelopmental outcomes of over 2500 NICHD network infants born <28 weeks and <1000 g. Male infants had significant increase in neurodevelopmental impairment at 18 to 22 months corrected age when compared with females.[27] Constable *et al*.,[28] using magnetic resonance imaging, found that former preterm male infants had lower white matter volume and poorer neuromotor integrity compared with term controls at 12 years of age. Our findings of male advantage in association with DCC are at odds with published data on male disadvantage for acute perinatal morbidity.

There is considerable speculation as to why male infants may be more susceptible to the negative effects of preterm birth. Derzbach *et al.*[29] proposes that the influence of estrogen may offer a protective effect to female infants even at an early age. Frazier and Werthammer[30] report that male infants are 2.5 times more likely to need resuscitation at birth when compared with females. Our findings suggest that there is a protective effect from placental transfusion through a brief delay (30 to 45 s) in cord clamping at birth for VLBW infants. The extra newborn blood volume seems to offer gender-specific, neuroprotective and immunoprotective benefit. It is possible that the effect is the result of an increased blood, red cell and stem cell volume, which may be more important for male than female infants.[14] These findings are of considerable interest as the evidence of gender-specific differences in VLBW infants continues to unfold.

The sample size of this study is a limitation; yet, currently this is the largest clinical trial published in the literature on VLBW infants and DCC with developmental follow-up. Assessments of outcomes at 7 months corrected age are limited in interpretation. However, we were constrained by our 3-year funding mechanism. The wide age range of infants at assessment is offset by the fact that the BSID are age adjusted. Thus any difference in performance due to age should be eliminated. Although most studies of preterm infants follow the children from 18 to 24 months, it is suggested that 4 years of age when motor outcomes stabilize and cerebral palsy can be confirmed may be optimal.[22] Our compliance rate for our primary outcome of BSID–II motor score is consistent with the literature.[31]

In summary, DCC at birth seems to be protective of VLBW male infants against motor disability at 7 months corrected age. Delaying the clamping of the cord for just 30 to 45 s while lowering the infant is a simple perinatal intervention which may offer a gender-specific benefit for improved motor outcome among the VLBW infants. Further research to replicate these findings is essential.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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