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Delayed Cord Clamping and Inotrope Use in Preterm Infants

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Abstract

Objective—To evaluate the impact of delayed cord clamping (DCC) on need for inotropic support and mean arterial blood pressure (MABP).

Methods—This is a single-center, prospective case-control study of premature infants, born <32 weeks gestation, who underwent DCC in comparison to a matched control group who underwent immediate cord clamping (ICC). The primary outcomes were the differences in MABP and inotropic medication use over the first week of life. Secondary outcomes included admission hemoglobin, need for blood transfusion, and rates of intraventricular hemorrhage (IVH). Infants were matched on EGA, birth weight, sex, antenatal corticosteroid and magnesium exposure, and presence of chorioamnionitis.

Results—158 infants (DCC n=79, ICC n=79) were included. Demographic factors were similar between groups. DCC infants had a higher admission hemoglobin ($p<0.01$), reduced incidence of high-grade IVH ($p=0.03$), fewer median transfusions ($p=0.03$), and were discharged at an earlier post-menstrual age ($p=0.04$). When controlling for other factors, DCC was not associated with a reduction in inotrope use ($p=0.22$) but was associated with a reduction in high-grade IVH ($p=0.01$). There was no difference in MABP between the groups.

Conclusions—DCC is not associated with a reduction in the use of inotropes or a difference in mean arterial blood pressure.

Keywords

Delayed cord clamping; prematurity; inotropes; hypotension; intraventricular hemorrhage

Introduction

Delayed cord clamping (DCC) is defined as a delay of at least 30 seconds between the delivery of the infant and clamping of the umbilical cord [1]. Although recommendations for

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a delay between birth and ligation of the umbilical cord can be found in medical literature going back several thousand years, immediate clamping (ICC) of the cord has been the general convention in modern medical practice [2]. Recent research [3–12] suggesting wide-ranging benefits of DCC has reignited an interest in this forgotten practice, both in the term and preterm infant. While the beneficial effects of DCC are less apparent in the term infant [13], the 2012 meta-analysis by Rabe et al. [1] demonstrated beneficial effects in preterm infants including a reduction in the need for transfusions, decreased risk of intraventricular hemorrhage (IVH) of any grade and a decreased risk for necrotizing enterocolitis, although these findings are based on many studies with small sample size groups ($n < 20$) and recent larger randomized trials have called into question some of these effects [9].

A particular area of focus is the hemodynamic changes induced by delayed cord clamping. The increased intravascular volume may be associated with decreased incidence of hypotension and a reduction in the use of inotropic medications (such as dopamine or epinephrine), both of which have been linked to the development of IVH [14]. Despite this potential for benefit, the hemodynamic effects of DCC have had limited investigation: to date only five studies have evaluated the impact of DCC on the use of inotropic medications. Three studies demonstrated no difference in use of inotropes by group [3,7,10]. Two additional studies [6,15] demonstrated a significant difference in inotrope use between groups, although both studies utilized umbilical cord milking (which may have different effects in and of itself [16]) and had much higher rates of inotrope administration than is typically used [17], 30–85%).

Furthermore, many DCC studies cited in recent meta-analyses are a decade or more old [1,18]. Pediatric and Obstetric practices have improved significantly over that time period, particularly the widespread use of antenatal corticosteroids, more limited invasive mechanical ventilation, and the implementation of IVH prevention “bundles” (i.e. a collection of clinical care practices designed to reduce the incidence of IVH, such as midline head position for 72h, prevention of hypothermia, prevention of hypo- and hypercarbia, etc.) [19], potentially calling into question the durability of the effect of DCC. Other studies have focused predominately on perinatal and outcome factors, with limited focus on the impact of the postnatal clinical course. Although factors which lead to hemodynamic compromise (e.g. pneumothorax, pericardial tamponade) are linked to hypotension and are well-established risk factors for the development of IVH [20], the interaction between these events and the potentially beneficial effects of DCC are unclear.

In this study, we compare a group of infants who received DCC in comparison to a carefully matched contemporaneous group of infants who received immediate cord clamping (ICC). The primary outcomes were the differences in the use of inotropic medications and the MABP over the first week of life. Secondary outcomes included admission hemoglobin, number of blood transfusion, rates of intraventricular hemorrhage, and the durability of DCC as a neuroprotective factor in the setting of an acute hemodynamically compromising event.

Patients and Methods

Patient selection – DCC group

A delayed cord clamping protocol was initiated at Barnes-Jewish Hospital in April 2014 for all infants born before 32 completed weeks of gestation. Prior to time point, all infants underwent ICC. Exclusion criteria consisted of: (1) multiple gestation pregnancy, (2) sonographic evidence of intrauterine growth restriction (estimated fetal weight < 10th centile) with absent or reversed end-diastolic blood flow, (3) placental abnormalities (i.e. placenta previa, abruptio or accreta), and/or (4) severe maternal anemia prior to the start of the delivery (hemoglobin < 7 g/dL). Comprehensive maternal and infant characteristics were prospectively collected from the outset of protocol initiation.

Patient selection – ICC group (control)

A control group of infants was derived from an existing dataset of inborn infants enrolled in an ongoing longitudinal monitoring study, conducted during a contemporaneous time period, who were born prior to the implementation of the DCC protocol (2012–2014). Infants in the control group were matched for gestational age, birth weight, sex, antenatal corticosteroid and magnesium exposure, and presence of chorioamnionitis (pathologic diagnosis).

Infant and maternal characteristics

All infants were admitted to the NICU at St. Louis Children's Hospital, a level IV unit which serves an urban, suburban, and rural population. Comprehensive maternal/perinatal, patient and clinical factors were collected. Maternal/perinatal factors included mode of delivery, antenatal magnesium sulfate exposure, antenatal corticosteroid exposure, diagnosis of pre-eclampsia, chorioamnionitis (pathologic diagnosis), arterial cord blood gas pH, length of DCC, and the five-minute Apgar score. Patient factors included gestational age in completed weeks, birth weight, intrauterine growth restriction status (defined as birth weight < 10th centile), sex, and race/ethnicity. Clinical factors included CRIB-II score (using the algorithm developed by Parry et al.[21]), admission temperature, the presence or absence of an acute hemodynamically compromising event (defined as CPR in the delivery room, pneumothorax, spontaneous intestinal perforation and/or pericardial tamponade), intraventricular hemorrhage (graded using the Papile scoring system[22]), hemoglobin concentration at admission (obtained from central line), need for inotrope use in the first week of life (inclusive of dopamine, dobutamine, epinephrine, and norepinephrine), need for normal saline volume expansion in the first week of life, use of hydrocortisone for treatment of refractory hypotension, need for transfusion during hospitalization, mortality rate, and post-menstrual age (PMA) at the time of discharge.

Institutional practices

Delayed cord clamping—For delayed cord clamping, the Obstetric and Pediatric teams discussed the patient prior to delivery to ensure agreement on the inclusion criteria. Once the infant was delivered, he/she was held at the level of the perineum (vaginal delivery) or placed on the mother's legs (Cesarean delivery). The Pediatric team operated the timer and called out the elapsed time in 15-second intervals. The goal delay time was between 30 and

45 seconds. Once 30 seconds was reached, the umbilical cord was doubly-clamped and then cut. The infant was handed over to the Pediatric team and resuscitation proceeded. During the delay period, the infants were gently stimulated by the Obstetric team to encourage respiration. Temperature management strategies included raising the room temperature to 25°C and placement of the infant on the mother abdomen.

Hypotension management—For blood pressure support, our institutional practice is to consider inotrope initiation when either (a) the mean arterial blood pressure (MABP) < EGA in weeks, (b) there is poor urine output (< 1 mL/kg/h) and/or (c) there are clinical signs of poor perfusion (prolonged central capillary refill time) or tachycardia). Dopamine is used as the first-line agent, with a starting dose between 2.5 and 5 mcg/kg/min. Dobutamine or norepinephrine can be added as second-line treatments when there is inadequate response to dopamine (when dosing exceeds 10 mcg/kg/min). Additionally, hydrocortisone, dosed at 1 mg/kg every 8 hours, can be added as an alternative second-line treatment for refractory hypotension. Volume resuscitation with normal saline can be given prior to or in conjunction with inotropic support and is administered in 10 mL/kg aliquots. There were no changes in institutional guidelines or practices for the management of hypotension over the entire study period.

Blood transfusion—Institutional protocol is to transfuse acutely ill preterm infants when the hemoglobin is less than 10 g/dL or infants with symptomatic anemia (e.g. apnea) when the hemoglobin is less than 8 g/dL. Transfusions are given in 15 mL/kg aliquots over a 2-hour period. Prior to the first transfusion, blood from a single donor is portioned and saved for future transfusions to reduce donor exposure.

Cranial ultrasound—For premature infants, our institutional practice is to obtain cranial ultrasound examinations at least once in the first three days of life and again at seven days of life, encompassing the periods of greatest risk. All studies include coronal and sagittal views through the anterior fontanelle and examination of the posterior fossa (to detect cerebellar hemorrhage) through the mastoid window.

Blood pressure data

Longitudinal blood pressure data from the first week of life was collected for all infants who had an umbilical arterial catheter. Given problems with the reliability of non-invasive blood pressure measurements [23], only infants who had blood pressure measurements made by intra-arterial catheter were included for both the DCC and ICC groups. Our institutional practice is to attempt placement of umbilical arterial catheters at the time of hospital admission in all infants at risk for hypoxic respiratory failure (as indicated by high levels of ventilator support and/or supplemental oxygen requirement). All catheters are placed in the descending thoracic aorta, located between the sixth and eighth vertebral body on chest radiograph. Blood pressure measurements were extracted from the electronic medical record using a searchable database (Clinical Investigation Data Exploration Repository, CIDER) maintained by Washington University's Center for Biomedical Informatics. Measurements were aligned by postnatal age and averaged in 3 hour epochs over the first seven days of life.

The length of the study window (seven days) was chosen to encompass three distinct sources of hemodynamic instability in the preterm infant: difficulty transitioning from the intrauterine environment (first 24–48 hours), persistently patent ductus arteriosus (3rd–4th day of life), intraventricular hemorrhage (greatest risk in the first 7 days).

Statistical methodology

Given the discrepancy in effect size of DCC and the use of inotropes in the existing literature, *a priori* power calculations could not be made. Univariate comparisons were made between the DCC and the ICC group using the Mann–Whitney U-test for continuous variables or Fisher's Exact Test (two-sided) for categorical variables.

Binary logistic regression models were constructed for the prediction of inotrope use using known or plausible covariates including gestational age, birth weight, antenatal steroids, chorioamnionitis, acute hemodynamic compromising event, PDA requiring medical or surgical treatment, and delayed cord clamping. Similarly, binary logistic regression models were constructed for the prediction of IVH of any grade and high grade IVH (grade III or IV diagnosed on cranial ultrasound in the first 7 days of life using the Papile classification[22]). Known and plausible risk factors for the development of IVH were included in the model including gestational age, birth weight, antenatal steroids, acute hemodynamic compromising event, inotrope use, mode of delivery, and delayed cord clamping. The Wald Z-statistic was calculated for each variable to provide standardized estimate of the strength of association of each covariate included in the models.

A generalized linear model was constructed to evaluate the impact of delayed cord clamping on the number of blood transfusions. Known or plausible risk factors for blood transfusion were included in the model including gestational age, birth weight, acute hemodynamic compromising event, PDA requiring medical or surgical treatment, IVH of any grade, necrotizing enterocolitis, and delayed cord clamping. The standardized beta coefficient was then calculated for each covariate to allow for comparison of effect size for each covariate.

For all models, the variance inflation factor (VIF) was calculated for all covariates to assess for collinearity (defined as $VIF > 5$). Results were considered statistically significant for all $p < 0.05$. Statistical analysis was conducted using R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).

The study design and procedures were approved by the Human Research Protection Office at Washington University.

Results

Sample characteristics

A total of 158 infants were included in the study, with 79 infants in the DCC group matched to 79 infants in the ICC control group. In terms of perinatal and demographic factors, there were no differences between the groups for mean gestational age, birth weight, sex, race, delivery method, pre-eclampsia, antenatal steroid or antenatal magnesium sulfate exposure,

chorioamnionitis, arterial cord blood pH, or Apgar score at 5 minutes. See Table 1 for an overview of the two groups.

In terms of clinical factors, the DCC group had higher hemoglobin at admission (15.4 vs. 14.1 g/dL, $p < 0.01$), lower rates of Grade III/IV IVH (5 vs. 16%, $p=0.03$), fewer total transfusions (median of 0 vs. 2, $p=0.04$) and was discharged at an earlier postmenstrual age (40.1 vs. 41.5 weeks, $p=0.05$). All other factors were not statistically significant. See Table 2 for complete results.

Blood pressure values

Arterial blood pressure data was available for 95/158 (60%) of infants. The MABP increased rapidly over the first two days of life in both groups, before levelling off between 34 and 36 mmHg. The blood pressure values of the two groups did not diverge at any point during the study window. See Figure 1 for graphical representation of the measured blood pressure values.

Regression modeling

In the binary logistic regression analysis, increasing gestational age ($p < 0.01$) was independently associated with a decreased need for inotropic support, while a hemodynamically compromising event ($p<0.01$) was associated with an increased need for inotropic support. IVH diagnosis of any grade was independently associated with a hemodynamically compromising event ($p<0.01$) and the need for inotrope use ($p<0.01$). Vaginal delivery ($p=0.02$) and a hemodynamically compromising event ($p<0.01$) were also associated with an increased risk of high-grade IVH. Although there was no association between DCC and IVH diagnosis of any grade ($p=0.88$), DCC was independently associated with a decreased rate of high-grade IVH ($p=0.01$). All other factors included in the regression model were not statistically significant.

Increasing gestational age at birth was associated with a decreased number of blood transfusions ($p<0.01$). Hemodynamic compromise, PDA requiring treatment, IVH and NEC were each independently associated with an increased number of transfusions. DCC was not independently associated with a decreased need for transfusion.

A complete overview of each of the regression models is shown in Table 3.

Discussion

In this prospective case-control study, delayed cord clamping in infants born before 32 weeks of gestation was not associated with a decrease in the use of inotropes or a difference in mean arterial blood pressure. DCC was associated with increased hemoglobin at admission, decreased rates of high-grade IVH, and hospital discharge at an earlier PMA. While some of these findings have been described by other researchers, this study is the first to demonstrate the effect of delayed cord clamping in a large cohort taking both perinatal and postnatal factors into account.

The binary logistic regression models reveal the strengths, and also the limitations, of DCC as a measure for improving outcomes in preterm infants. In the case of high-grade IVH, DCC provides a protective effect while another widely studied factor, antenatal corticosteroids, does not. This is likely the result of the high rate of antenatal steroid administration in the study population (95% in both groups) and is highly reflective of current obstetrical practice. While this result suggests that further increasing the rates of steroid administration may not result in a substantial change in IVH rates, it does suggest that DCC is an effective adjunctive treatment, with independent risk reduction on top of the benefit provided by antenatal corticosteroids.

It is also important to note the limitation of DCC for protection against high-grade IVH, highlighted by the similar z-scores (although in opposite directions) for DCC and hemodynamically compromising events. This finding suggests that the beneficial effects of DCC can be essentially erased by a profound acute clinical event such as a pneumothorax. While DCC itself is inexpensive and has not been associated with an adverse event profile for the preterm neonate, enthusiasm for potential benefits should be tempered by each patient's individual clinical course.

The blood transfusion regression model demonstrates that DCC does not ultimately reduce the number of needed transfusions in preterm infants, despite a small increase in hemoglobin at admission. Infants born at this gestational stage typically spend months in the hospital and are chronically phlebotomized in the course of obtaining routine laboratory studies. Furthermore, they are at high-risk for any number of complications, each of which combine to play a significantly greater role in the need for transfusion as compared to the small effect imparted by delayed cord clamping. It is possible that alternative approaches to delayed cord clamping, such as a longer delay or milking of the cord may provide a greater volume of red blood cells and provide more benefit, and such investigation is ongoing [5,16].

Finally, DCC shows an advantage in decreased length of hospital stay, when adjusting for gestational age at birth, with DCC infants going home almost a week earlier, despite both groups starting out at essentially the same gestational age. The most likely mechanism is the global reduction in severity of medical complexity, potentially the result of small improvements in inotrope use, number of transfusions, and reduction of severe IVH, the composite of which may delay establishment of normal newborn care (full oral feeding, thermoregulation, respiratory stabilization) and prolong hospitalization.

The mechanism by which DCC reduces high-grade IVH is less clear. While delayed clamping does increase the circulating blood volume as compared to those with ICC, infants with immediate cord clamping are not necessarily hypovolemic. The increased circulating volume may allow for an increased cardiac output, a factor known to be only weakly correlated with blood pressure [24], and results in more stable blood flow, particularly to the impaired autoregulatory function of the preterm brain, a possible factor in the development of IVH [25,26]. Further research into differences in cardiovascular and autoregulatory function between those with immediate and delayed cord clamping is needed to better define this mechanism.

Although data was collected prospectively, this study has the same limitations as all observational studies, namely that the clinical care was provided at the discretion of individual doctors. Additionally, although effort was made to match infants in the two groups across factors that are the most significant drivers of outcome (gestational age, birth weight and sex [27]) infants were not randomized to the groups. In this cohort, umbilical arterial lines were placed more often in the DCC group as compared to the ICC, despite an equivalent degree of illness severity (as indicated by CRIB-II scores). Although the reason for this is unclear, it is unlikely to be the result of a change in clinical practice, as historical data from 2012–2015 demonstrate stable rates of UAC placement over the study period (45, 46, 39, 41% of all admitted infants born < 32 weeks EGA, respectively).

Although the benefits of DCC should not be oversold, it has, not unreasonably, become the standard of care at many centers, further supported by recent ACOG guidelines [28]. This loss of equipoise effectively prevents any future randomized studies of DCC, making an observational study with matched cohorts the only feasible study design.

Conclusion

Delayed cord clamping in infants born before 32 completed weeks of gestation is associated with an increased hemoglobin concentration at admission, discharge home at an earlier post-menstrual age, and a reduced risk of high-grade IVH. DCC was not associated with a reduction in inotrope use, mean arterial blood pressure, or the total number of transfusions, even when controlling for key clinical variables.

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References

1. Rabe H, Diaz-Rossello JL, Duley L, et al. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev*. 2012;CD003248. [PubMed: 22895933]
2. Weeks A. Umbilical cord clamping after birth. *BMJ*. 2007; 335:312–313. [PubMed: 17703005]
3. Rabe H, Wacker A, Hülskamp G, et al. A randomised controlled trial of delayed cord clamping in very low birth weight preterm infants. *Eur J Pediatr*. 2000; 159:775–777. [PubMed: 11039135]

4. Strauss RG, Mock DM, Johnson KJ, et al. A randomized clinical trial comparing immediate versus delayed clamping of the umbilical cord in preterm infants: short-term clinical and laboratory endpoints. *Transfusion (Paris)*. 2008; 48:658–665.
5. Hosono S, Mugishima H, Fujita H, et al. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2008; 93:F14–19. [PubMed: 17234653]
6. Hosono S, Mugishima H, Fujita H, et al. Blood pressure and urine output during the first 120 h of life in infants born at less than 29 weeks' gestation related to umbilical cord milking. *Arch Dis Child Fetal Neonatal Ed*. 2009; 94:F328–331. [PubMed: 19221402]
7. Oh W, Carlo W, Fanaroff A, et al. Delayed cord clamping in extremely low birth weight infants - a pilot randomised controlled trial. *Pediatr Res*. 2002; 51:365–366.
8. Ultee CA, van der Deure J, Swart J, et al. Delayed cord clamping in preterm infants delivered at 34–36 weeks' gestation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2008; 93:F20–23. [PubMed: 17307809]
9. Mercer JS, Erickson-Owens DA, Vohr BR, et al. Effects of Placental Transfusion on Neonatal and 18 Month Outcomes in Preterm Infants: A Randomized Controlled Trial. *J Pediatr*. 2016; 168:50–55.e1. [PubMed: 26547399]
10. McDonnell M, Henderson-Smart DJ. Delayed umbilical cord clamping in preterm infants: a feasibility study. *J Paediatr Child Health*. 1997; 33:308–310. [PubMed: 9323618]
11. Bhatt S, Alison BJ, Wallace EM, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. *J Physiol*. 2013; 591:2113–2126. [PubMed: 23401615]
12. Elimian A, Goodman J, Escobedo M, et al. Immediate compared with delayed cord clamping in the preterm neonate: a randomized controlled trial. *Obstet Gynecol*. 2014; 124:1075–1079. [PubMed: 25415157]
13. McDonald SJ, Middleton P, Dowswell T, et al. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev*. 2013;CD004074. [PubMed: 23843134]
14. Lee JY, Kim HS, Jung E, et al. Risk Factors for Periventricular-Intraventricular Hemorrhage in Premature Infants. *J Korean Med Sci*. 2010; 25:418. [PubMed: 20191041]
15. Patel S, Clark EAS, Rodriguez CE, et al. Effect of umbilical cord milking on morbidity and survival in extremely low gestational age neonates. *Am J Obstet Gynecol*. 2014; 211:519.e1–7. [PubMed: 24881823]
16. Katheria AC, Truong G, Cousins L, et al. Umbilical Cord Milking Versus Delayed Cord Clamping in Preterm Infants. *Pediatrics*. 2015; 136:61–69. [PubMed: 26122803]
17. Burns ML, Stensvold HJ, Risnes K, et al. Inotropic Therapy in Newborns, A Population-Based National Registry Study. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc*. 2016
18. Raju TNK. Timing of umbilical cord clamping after birth for optimizing placental transfusion. *Curr Opin Pediatr*. 2013; 25:180–187. [PubMed: 23407180]
19. Carreaux P, Cohen H, Check J, et al. Evaluation and development of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. *Pediatrics*. 2003; 111:e489–496. [PubMed: 12671169]
20. Volpe, JJ. *Neurology of the newborn*. 5th. Philadelphia: Saunders/Elsevier; 2008.
21. Parry G, Tucker J, Tarnow-Mordi W. CRIB II: an update of the clinical risk index for babies score. *Lancet*. 2003; 361:1789–1791. [PubMed: 12781540]
22. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978; 92:529–534. [PubMed: 305471]
23. Dannevig I, Dale HC, Liestøl K, et al. Blood pressure in the neonate: three non-invasive oscillometric pressure monitors compared with invasively measured blood pressure. *Acta Paediatr Oslo Nor* 1992. 2005; 94:191–196.

24. Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. *J Pediatr*. 1996; 129:506–512. [PubMed: 8859256]
25. Soul JS, Hammer PE, Tsuji M, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res*. 2007; 61:467–473. [PubMed: 17515873]
26. Vesoulis, ZA., Liao, SM., Trivedi, SB., et al. A Novel Method for Assessing Cerebral Autoregulation in Preterm Infants Using Transfer Function Analysis. *Pediatr Res* [Internet]. 2015. [cited 2015 Nov 16]; Available from: <http://www.nature.com/doifinder/10.1038/pr.2015.238>
27. Stevenson DK, Verter J, Fanaroff AA, et al. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. *Arch Dis Child Fetal Neonatal Ed*. 2000; 83:F182–185. [PubMed: 11040165]
28. Committee Opinion No. 684: Delayed Umbilical Cord Clamping After Birth. *Obstet Gynecol*. 2017; 129:e5–e10. [PubMed: 28002310]

Figure 1. Longitudinal mean arterial blood pressure values over the first 7 days of life. Each point represents the average of 3 hours of data. ICC group is shown with open circular markers while the DCC group has filled diamond markers. Whiskers represent ± 1 SEM.

Table 1

Perinatal and demographic factors

	ICC (n=79)	DCC (n=79)	P value
Gestational age, mean (SD), weeks	26.7 (1.8)	27.1 (2.2)	0.13
Birth weight, mean (SD), grams	957.2 (262.6)	1022.6 (326.3)	0.29
IUGR status ^a , n (%)	11 (14)	10 (13)	1.00
Male sex, n (%)	40 (51)	45 (57)	0.52
Race/Ethnicity			
Asian, n (%)	3 (4)	0 (0)	0.16
Black, n (%)	33 (42)	37 (47)	
Hispanic, n (%)	0 (0)	2 (3)	
White, n (%)	43 (54)	40 (50)	
Vaginal delivery, n(%)	21 (27)	32 (41)	0.09
Antenatal MgSO ₄ exposure, n (%)	64 (81)	70 (89)	0.27
Antenatal steroid exposure			
Any exposure, n (%)	75 (95)	75 (95)	1.00
Complete course ^b , n (%)	54 (68)	61 (77)	0.28
Pre-eclampsia, n(%)	22 (28)	33 (42)	0.09
Chorioamnionitis ^c , n (%)	23 (29)	13 (16)	0.09
Arterial cord blood pH, mean (SD)	7.30 (0.08)	7.31 (0.07)	0.22
Apgar score 5 min, median (range)	6 (1–9)	6 (1–9)	0.42
Length of delay before DCC, median (range), seconds	n/a	40 (30–51)	n/a

Footnote:

* Denotes significance at $p < 0.05$. Comparisons were made using Mann–Whitney U-test for continuous variables or Fisher’s Exact Test (two-sided) for categorical variables. Reported p values are unadjusted.

^aDefined as birth weight < 10th centile.

^bDefined as two doses over a 48-hour period.

^cBased on histopathologic diagnosis.

Table 2

Clinical Factors

	ICC (n=79)	DCC (n=79)	P value
Admission temperature, mean (SD), °C	36.9 (0.6)	36.9 (0.7)	0.40
Hemoglobin at admission, mean (SD), g/dL	14.1 (2.1)	15.4 (2.6)	<0.01*
CRIB-II score, median (range)	10 (2–15)	9 (2–19)	0.15
Hemodynamically compromising event			
CPR in delivery room, n (%)	9 (11)	6 (8)	0.41
Pneumothorax, n (%)	2 (3)	2 (3)	1.00
Spontaneous intestinal perforation, n (%)	4 (5)	4 (5)	1.00
Pericardial tamponade, n (%)	1 (1)	1 (1)	1.00
Any, n (%)	12 (15)	8 (10)	0.47
Hemodynamically significant PDA ^a , n (%)	27 (34)	18 (23)	0.15
Intraventricular hemorrhage			
Any grade, n (%)	20 (25)	18 (23)	0.85
Grade III/IV, n (%)	13 (16)	4 (5)	0.03*
Inotrope use, n (%)	21 (27)	15 (19)	0.34
Hydrocortisone use for inotrope-resistant hypotension, n (%)	4 (5)	4 (5)	1.00
Volume expansion			
Any fluid bolus, n (%)	21 (27)	15 (19)	0.34
No. fluid boluses, median (range)	0 (0–12)	0 (0–5)	0.33
Blood transfusions			
Any transfusion, n (%)	51 (65)	39 (49)	0.07
No. transfusions, median (range)	2 (0–15)	0 (0–18)	0.04*
Died, n (%)	5 (6)	8 (10)	0.56
NEC, n (%)	7 (9)	6 (8)	1.00
PMA at discharge, mean (SD), weeks	41.5 (5.2)	40.1 (5.4)	0.04*

Footnote:

* Denotes significance at $p < 0.05$. Comparisons were made using Mann–Whitney U-test for continuous variables or Fisher’s Exact Test (two-sided) for categorical variables. Reported p values are unadjusted.

^a Defined as need for medical or surgical management.

Table 3

Regression models by outcome

Inotrope use			
	Wald Z statistic	P value	VIF
EGA	−3.26	<0.01 *	1.94
BW	−0.45	0.65	1.71
Antenatal steroids	0.01	0.99	1.00
Chorioamnionitis	0.32	0.75	1.10
Hemodynamic compromise	3.11	<0.01 *	1.19
PDA requiring treatment	−0.01	0.99	1.15
Delayed cord clamping	−1.24	0.22	1.08
IVH (any grade)			
	Wald Z statistic	P value	VIF
EGA	−0.81	0.42	3.70
BW	1.68	0.09	3.53
Antenatal steroids	0.34	0.73	1.05
Hemodynamic compromise	3.42	<0.01 *	1.10
Inotrope use	3.66	<0.01 *	1.65
Vaginal delivery	0.74	0.46	1.19
Delayed cord clamping	0.15	0.88	1.10
High-grade IVH			
	Wald Z statistic	P value	VIF
EGA	−1.40	0.16	3.05
BW	1.49	0.14	3.06
Antenatal steroids	0.01	0.99	1.00
Hemodynamic compromise	2.58	<0.01 *	1.67
Inotrope use	2.64	<0.01 *	1.61
Vaginal delivery	2.26	0.02 *	1.42
Delayed cord clamping	−2.56	0.01 *	1.32
Number of transfusions			
	Standardized Beta Coef.	P value	VIF
EGA	−0.48	<0.01 *	3.08
BW	−0.02	0.78	3.08
Hemodynamic compromise	0.19	<0.01 *	1.28
PDA requiring treatment	0.14	<0.01 *	1.24
IVH	0.15	<0.01 *	1.28
NEC	0.37	<0.01 *	1.10

Inotrope use			
	Wald Z statistic	P value	VIF
DCC	0.03	0.56	1.03

Footnote:

* Denotes significance at $p < 0.05$. VIF- variance inflation factor.