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Complete List of Authors:	Mercer, Judith S.; University of Rhode Island, Nursing, Midwifery; , Vohr, Betty R.; Brown Medical School, Pediatrics McGrath, Margaret; University of Rhode Island, Nursing Padbury, James F.; Brown Medical School, Pediatrics Wallach, Michael; Brown Medical School, Radiology Oh, William; Brown Medical School, Pediatrics
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Delayed Cord Clamping In Very Preterm Infants Reduces the Incidence of Intraventricular Hemorrhage and Late Onset Sepsis: A Randomized Controlled Trial

Judith S. Mercer, DNSc, CNM
University of Rhode Island, Kingston, RI

Betty R. Vohr, MD
Brown Medical School, Providence, RI

Margaret M. McGrath, DNSc
University of Rhode Island, Kingston, RI

James F. Padbury, MD
Brown Medical School, Providence, RI

Michael Wallach, MD
Brown Medical School, Providence, RI

William Oh, MD
Brown Medical School, Providence, RI

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Judith S. Mercer, DNSc
Professor, College of Nursing
University of Rhode Island,
2 Heathman Road,
Kingston, RI 02881
401-874-5303, Fax 401-874-2870
jmercer@uri.edu

Statistical Consultation: Jenifer Allsworth, Ph.D., Division of Research, Department of Obstetrics and Gynecology, Women and Infants Hospital, Providence, Rhode Island and Yeong Kwak, R.N., Ph.D., University of Connecticut School of Nursing, Storrs, Connecticut.

CONDENSATION

The simple intervention of delayed cord clamping while lowering the infant appears to reduce the incidence of intraventricular hemorrhage and late onset sepsis in VLBW infants.

Abbreviations

BPD – bronchopulmonary dysplasia
CUS – cranial ultrasound
DCC – delayed cord clamping
ICC – immediate cord clamping
IVH – intraventricular hemorrhage
LOS – late onset sepsis
NEC – necrotizing enterocolitis
NICU – Neonatal Intensive Care Unit
PIH – pregnancy induced hypertension
ROP – retinopathy of prematurity
SNEC – suspected necrotizing enterocolitis
VLBW – very low birth weight

ABSTRACT

OBJECTIVE

This study compared the effects of immediate (ICC) and delayed (DCC) cord clamping on VLBW infants on two primary variables: bronchopulmonary dysplasia (BPD) and suspected necrotizing enterocolitis (SNEC). Other outcome variables were late onset sepsis (LOS), and intraventricular hemorrhage (IVH).

STUDY DESIGN

This was a randomized controlled unmasked trial in which women in labor with singleton fetuses less than 32 weeks gestation were randomized to ICC (cord clamped at 5 to 10 seconds) or DCC (30 to 45 seconds). Women were excluded for the following reasons: their obstetrician refused to participate; major congenital anomalies; multiple gestations; intent to withhold care; severe maternal illnesses; placenta abruption or previa; or rapid delivery after admission.

RESULTS

Seventy-two mother/infant pairs were randomized. Infants in the ICC and DCC groups weighed 1151 (± 379) and 1175 (± 346), and mean gestational ages were 28.2 (±2.4) and 28.3 (± 2.1) weeks respectively. Analyses revealed no difference in maternal and infant demographic, clinical and safety variables. There were no differences in the incidence of our primary outcomes (BPD and suspected NEC). However, significant differences were found between the ICC and DCC groups in the rates of IVH (36% vs. 14%, p = 0.03) and LOS (22% vs. 3%, p = 0.03). Two (9%) of the 23 male infants in the DCC group had IVH versus 8 (42%) of the 19 in the ICC group (OR 0.43, CI 0.24 to 0.76, *p* = .026). No cases of sepsis occurred in the 23 boys in the DCC group while six (32%) of the 19 boys in the ICC group had confirmed sepsis (p = .005). There was a trend towards higher initial hematocrit in the infants in the DCC group (49 ± 6 versus 46 ± 6, *p* = .06).

CONCLUSION

Delayed cord clamping appears to protect VLBW infants from IVH and LOS especially for male infants.

Key Words: delayed cord clamping, intraventricular hemorrhage, IVH, late onset sepsis, VLBW infants, randomized controlled trial

INTRODUCTION

The current obstetrical practice in the United States is to clamp the umbilical cord of the very low birth weight (VLBW) infant immediately after delivery.[1] However, delaying cord clamping and lowering the infant below the perineum or incision site at cesarean section have been shown to significantly increase transfer of blood from the placenta to the infant.[2, 3] A delay of 30 to 45 seconds in cord clamping of preterm infants results in an 8 to 24% increase in blood volume (2 to 16 ml/kg after cesarean birth and a 10 to 28 ml/kg after vaginal birth).[4] Immediate cord clamping may deprive the VLBW infant of essential blood volume and create a state of potential circulatory compromise[5] resulting in hypotension,[6 7, 8] and poor perfusion of tissues.[9,10]

Nine randomized controlled trials over the last decade have documented the safety and efficacy of delayed cord clamping in low birth weight or very low birth weight infants.[11] Benefits include higher blood pressure,[7, 12] higher hematocrit levels,[13-15] more optimal oxygen transport and higher red blood cell flow,[10] fewer days on oxygen and ventilation,[16] fewer transfusions,[14, 16] and lower rates of IVH.[17, 18] Previous studies of cord clamping interventions, however, have been limited by small sample size, inconsistent definition of variables, and lack of follow-up beyond 6 weeks.[11]

In a prior pilot study, we validated the feasibility and safety of the protocol for delayed cord clamping as well as immediate and short-term physiologic advantages of DCC.[8] Findings included higher initial blood pressure, less suspected necrotizing enterocolitis, and fewer infants discharged on oxygen. Based on this pilot data, we hypothesized that the additional red blood cells obtained by delaying cord clamping may result in lower incidence of bronchopulmonary dysplasia (BPD).

The objective of this study was to compare the incidence of BPD in infants < 32 weeks gestation randomized to early (< 10 seconds) and late (30 to 45 seconds) cord clamping. The study was also designed to evaluate the effects of delayed cord clamping on other neonatal morbidities including suspect necrotizing enterocolitis (SNEC), late onset sepsis (LOS), intraventricular hemorrhage (IVH), and retinopathy of prematurity (ROP).

MATERIALS AND METHODS

This randomized controlled trial was conducted between August 2003 and December 2004 at Women and Infants' Hospital of Rhode Island (WIH). The study was approved by the Institutional Review Boards at WIH and the University of Rhode Island. An independent data safety and monitoring committee consisting of a maternal-fetal medicine obstetrician, a neonatologist, a nurse physiologist and a nurse statistician reviewed the data after 14, and again, after 50 patients were randomized.

The primary outcome variable was bronchopulmonary dysplasia (BPD) and the secondary outcome variables were SNEC, IVH, LOS and ROP. Other outcome variables included: Apgar scores, temperature on arrival in the NICU, the highest serum bilirubin level, initial and hourly blood pressures for four hours, initial hematocrit, and need for blood transfusion during the infant's hospital stay.

All women admitted between 24 and 31.6 weeks gestation with preterm labor were candidates for inclusion in the study. The gestational age assessment using last menstrual period and/or early pregnancy ultrasound was used to establish eligibility for the study. Exclusion criteria included: obstetrician's refusal to participate, major congenital anomalies or multiple gestations, intent to withhold care, severe maternal illnesses, or placenta abruption or previa. Women had to be admitted to the hospital at least 2 hours before delivery to allow time for enrollment. Once a potential subject was identified, approval of the attending obstetrician was obtained, the mother was approached, and written informed consent was obtained.

A statistician who was not involved in the trial developed a computer-generated random number system. Block stratified randomization was used to assign the intervention to the subjects above and below 28 weeks with a pre-specified equal probability to avoid unequal numbers of participants in each gestational age group. Two sets of cards labeled for randomization were enclosed in sequenced, opaque envelopes containing group assignment and kept in the Labor Unit. Research assistants who were registered nurses and the PI (JSM) shared an on-call schedule to screen potentially eligible women, enroll them, and attend the births. When called for a subject's impending birth, the PI or RN opened the next randomization card, informed the staff of the group assignment, reviewed the protocol with the attending obstetrician, attended the birth, and timed the cord clamping.

Women were assigned to receive either immediate cord clamping (ICC) or delayed cord clamping (DCC). For the ICC group, the obstetrician clamped the umbilical cord immediately (<10 seconds) after

birth. For the DCC group, the obstetrician clamped the cord at 30 to 45 seconds and held the infant in a sterile towel or blanket approximately 10-15 inches below the mother's introitus at vaginal delivery or below the level of the incision at cesarean section. Care was taken that no tension or traction was placed on the cord. A stopwatch was used to mark the time when the infant's buttocks were delivered from the vagina or the uterus (or head if breech) and then the time elapsed was counted out in ten second intervals for the obstetrician. At 30 to 45 seconds, the obstetrician clamped and cut the umbilical cord, and the infant was moved to the radiant warmer for care. Infants in both groups were supplied with an additional warming mattress (Transwarmer Infant Mattress, Cooper Surgical, Trumbull, CT) to assist in maintaining temperature. The obstetricians could alter the protocol based on their clinical judgment although this event did not occur throughout the course of the study. In the event that the timing of0 the cord clamping was less than 30 seconds and the baby was randomized to the DCC group, a protocol violation report was completed and the infant remained in the late clamped group (intention-to-treat).

The subsequent clinical management of the infants was at the discretion of the attending neonatologists. Because of the obvious nature of the intervention, the study could not be blinded. Our institutional policy requires the presence of a pediatric staff member because of low gestation. However, staff that attended each birth adhered to the PI's request not to reveal the infant's grouping in the infant's medical records.

Prenatal and delivery data were collected from the mothers' charts. Time of cord clamping, placement of the infant, Apgar scores, and time and date of birth were collected in the Labor Unit. Infant data were collected after 12 hours of age and after discharge. BPD was defined as requiring oxygen therapy up to 36 weeks postmenstrual age or death. SNEC was defined as clinical impression when the neonatology staff ordered an x-ray to rule out NEC and the infant was made NPO for at least 24 hours. Cranial ultrasound (CUS) readings used the grading system of Papile: grade 1 is a germinal matrix hemorrhage; grade 2 is extension into the lateral ventricle with blood filling less than 50% of the ventricular area; Grade 3 is IVH with distension or dilatation of the lateral ventricles with blood; and Grade 4 is IVH with parenchymal involvement. CUS were read by a single pediatric radiologist (MW) who was blinded to the infant's grouping. Late onset sepsis was defined as blood culture positive in infants > 72 hours of age. Necrotizing enterocolitis was diagnosed based on Bell's criteria[19] and retinopathy of

prematurity was identified by an ophthalmologist per our routine eye examinations during the infants stay in the nursery.

Power analysis was based on the event rate of bronchopulmonary dysplasia (56%) in the control group of our pilot study[8] with a 30% relative reduction that would result in a 39% event rate. An alpha level of .05, and a beta level of .20 with a medium effect size (r = .30), was used to determine that 26 babies were needed in each cord clamping interval group. An over sampling of 20% brought each group to 36 babies for a total of 72 subjects. All data were analyzed on an intention-to-treat basis. In spite of directional primary hypotheses, we used two-tailed tests to be as conservative as possible. Continuous variables were examined with Students t test and categorical variables were tested using Chi-square and Fisher's Exact test if cells contained counts less than 5. Logistic regression was used to control for gestational age and obtain odds ratios for significant findings.

RESULTS

Figure 1 shows the distribution of the 296 women who were admitted with preterm labor and who were screened for eligibility for this study. All further analyses were performed on the 72 randomized subjects.

There were 7 protocol violations. Six occurred in the DCC group with cord clamping time ranging between 2 and 18 seconds instead of 30 seconds. These were mainly as a result of miscommunication at births. There was one protocol violation in the ICC group when a physician delayed clamping for 25 seconds due to a misunderstanding of the protocol. All infants remained in their assigned groups for analyses.

Table I shows no significance difference in maternal demographics, clinical characteristics and medical management.

Table II shows no significant difference in the demographic and clinical characteristics of the study infants. Cord clamping time was significantly different per protocol—infants in the DCC group had significantly longer cord clamping times (32 seconds $\pm$ 13 vs. 7 seconds $\pm$ 4, $p < .001$). All other neonatal variables including those used for safety (1 and 5 minute Apgar scores, temperature on admission, serum bilirubin levels) were not significantly different between the groups.

Table III shows that there were no significant differences in the incidence of death or BPD, NEC, amount of blood loss and transfusion and ROP between the two groups.There were also no differences between the infants in surfactant use (27 versus 24), days of ventilation (39 versus 35) , and oxygen use at 28 days (11 versus 13) for the ICC and DCC groups respectively.

Table IV shows that infants in the DCC group had less IVH (5 [14%] versus 13 [36%], p = .03) during the first 28 days in the NICU. The incidence of IVH was equally divided between the stratified groups (< 28 wks = 10; 28 ± weeks = 8), although the majority occurred in infants less than 30 weeks gestation (data not shown). In the infants less than 28 weeks, 7 (47%) of the 15 infants in the ICC group had IVH versus 3 (21%) of the 14 infants in the DCC group (NS) while in those born after 28 weeks, 6 (29%) of 21 in the ICC group and 2 (10%) of 22 in the DCC group had IVH.

Similar number of infants in each group received low dose Indomethacin for IVH prophylaxis within the first 24 hours. All of the infants between 24 and 27 weeks had Indomethacin while 59 and 62% received Indomethacin in the DCC and ICC groups respectively. The Grade 4 IVH was not seen until day of life 12. One infant in the DCC group with IVH was a protocol violation and had immediate cord clamping.

We compared all infants with IVH (n = 18) with all infants without IVH (n = 54). Infants with IVH had shorter time between birth and cord clamping (13 seconds versus 22 seconds, p = 0.04) and were less likely to have had a cesarean delivery (3 [17%] vs. 15 [48%], p = 0.03). There was no relationship between IVH and sepsis.

Table IV shows that infants in the DCC group were less likely to have blood culture-proven sepsis during the NICU stay (3% vs. 22%, p = 0.03). Six cases of confirmed sepsis occurred in the 24 to 27 week infants while 3 were in infants 28 to 31 weeks. Of the 9 infants who had late onset sepsis, 7 (78%) occurred between 11 and 18 days of age. Infants with sepsis had lower initial hematocrit levels at birth (48 ± 6 versus 42 ± 5, p = .03) even when controlling for gestational age.

Analyses by gender revealed that male infants had an advantage with DCC for IVH, sepsis, and NEC. Gender effects are shown in Table 5.

There were no adverse events or deaths in the DCC group. Three infants died in the ICC group. The causes of death included fulminating NEC (2) and terminal respiratory failure with probable sepsis syndrome.

Further multivariate analyses were performed to evaluate the association of cord clamping with IVH and late onset sepsis. The impact of cord clamping group on IVH was evaluated adjusting for gestational age and cesarean section. The final model indicated that the IVH rate was more than 3 times higher in the ICC group (OR 3.5, 95% CI 1.1 – 11.1). A similar model for late onset sepsis adjusted for gestational age showed that infants in the DCC group were less likely to have sepsis (OR 0.10, 95% CI .01-.84).

The eligible women not enrolled during the study period did not differ from the 72 randomized participants on any of the demographic variables. They differed from randomized women only in antenatal steroid use (87% vs. 100%, p = 0.01), PROM in hours (20 $\pm$ 36 versus 40 $\pm$ 45, p = 0.01, and Cesarean section rate (64% versus 40%, p = 0.01). Infants of eligible women not enrolled differed from study infants only on admission temperature (96.3 $\pm$ 1.4 versus 97 $\pm$ 1.4, p = .01). There was no significant difference in the overall incidence of IVH (25% versus 18%, p = 0.35) or sepsis (3% versus 8%, p = 0.42) between the subjects and the infants of eligible women not enrolled.

DISCUSSION

Our primary null hypothesis was that infants in the DCC group would have the same rate of BPD based on the results from the pilot study. The null hypothesis proved to be true. The reason for the failure to reject the null hypothesis is that the study event rate of BPD in the ICC group (25%) turned out to be much lower than the event rate used for sample size calculation (56%) resulting in an underpowered estimate. The finding that DCC resulted in less IVH and less sepsis was unanticipated.

Our data indicates that a brief delay in cord clamping time accompanied by lowering the infant to hasten the placental transfusion offers protection from IVH and late onset sepsis. The fact that the groups had almost identical demographic and baseline characteristics shows that the randomization process was successful. As in our previous pilot study, this study provided evidence that the protocol does not put even the smallest infants at risk of harm.[8]

The theoretical foundation for the study was that the additional blood volume received as a result of DCC would help to reduce neonatal morbidity by providing more blood volume and improving cardiovascular stability. The preterm infant has less fetal-placental blood volume in his body at any point in time than the term infant making him more likely to have a deficit if immediate clamping occurs.[20] The high pressure in the placental circulation continues briefly after birth and fosters transfer of blood to the infant.[21]

The increase in cardiac output to the lung from 8% during fetal life to the 45% immediately after birth necessitates transfer of an adequate blood volume.[20] When the cord is clamped before an adequate placental transfusion to the infant has occurred, blood volume may be taken from other capillary beds resulting in relative hypoperfusion.[22] A potential circulatory effect of relative hypoperfusion may be disruption of the autoregulation essential to stabilize cerebral blood flow and prevent a pressure-passive circulation.[23] If the baby is not hemodynamically stable, there may be ischemic injury to the brain,[24] the GI tract and the lung.

Reduced blood volume does not necessarily result in immediately reduced blood pressure or lower hematocrit as the infant's cardiovascular system increases vascular resistance to stabilize blood pressure.[25] Increased capillary permeability in the preterm newborn allows rapid fluid shifts.[5] These factors, and lack of available accurate measurement techniques for blood volume, make hypovolemia difficult to verify in the newborn, even though its effect may be profound. DCC allows time for placental transfusion to supply essential blood volume to the infant and lowering the infant speeds the transfer of blood volume.[26]

The finding that IVH was higher in the immediately clamped group is consistent with the recent meta-analysis of RCTs on DCC in PT infants.[11] Other authors have reported reduced cerebral blood volume preceding development of IVH.[27, 28] Any reduction in IVH is important because of its association with later morbidity, mortality and/or developmental delay.[29] Even Grades I and 2 are not without sequelae.[30]

Our nursery practiced prophylactic Indomethacin to prevent IVH based on the study of Ment et al.[31] However, the number of infants receiving this intervention was similar between the two study groups.

All the infants with confirmed late onset sepsis (LOS) had immediate cord clamping. The one listed for the DCC Group was a protocol violation and her cord was clamped at 3 seconds. This finding is important as LOS continues to be an important cause of morbidity and mortality in the NICU and neurodevelopmental delay.[32] We speculate that sepsis may be a result of immuno-compromise due to loss of protective primitive hematopoietic progenitor cells along with blood volume at birth. The cord blood of preterm infants (24-31 weeks) contains the highest concentration of primitive hematopoietic progenitor cells and long-term culture-initiating cells when compared to the cord blood of infants closer to term.[33]

The apparent protective effect of delayed cord clamping for the male infants suggests the hypothesis that the additional blood volume the infant obtains may have gender-specific neuroprotective and immunoprotective effects. This finding is of interest since there is increasing evidence of gender-specific differences in neonates. For example, indomethacin, has been shown to exhibit gender-specific effects on cerebrovascular reactivity, which were associated with a significantly decreased rate of IVH in boys.[34]

Limitations of this study are that the primary null hypothesis was accepted because the study was underpowered due to the use of a high event rate from our pilot study and the rejection of secondary null hypothesis that is unanticipated. Nonetheless, the fact that our findings are consistent with the result of the recent meta-analysis,[11] strengthens the idea that these findings are generalizable to the population of very low birth weight preterm infants. This study adds to the growing body of knowledge on the benefits of delayed cord clamping in preterm infants.[11] It may be that the small amounts of addition blood preterm infants obtain by delaying cord clamping helps to stabilize cerebral blood flow, autoregulation, increase oxygen delivery to vulnerable tissues, prevent ischemia, and cytokine release, and provide additional stem cells to establish adequate immunocompetence.

We have demonstrated that a brief delay in cord clamping time, accompanied by lowering the infant to hasten the placental transfusion, offers protection from IVH and late onset sepsis. The innovation of this study is the simplicity of the intervention of delaying cord clamping 30 to 45 seconds and lowering the infant. The additional blood volume received appears to contribute to the improved outcomes of tiny preterm infants.

REFERENCES

1. Bloom RS, Cropley C, Committee AANRPS. Textbook of Neonatal Resuscitation. Illinois: American Academy of Pediatrics; 1995.

2. Yao AC, Lind J, Tiisala R, Michelsson K. Placental transfusion in the premature infant with observation on clinical course and outcome. Acta Paediatr Scand 1969;58(6):561-6.

3. Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. Lancet 1969;2(7626):871-3.

4. Narenda A, Beckett CA, T., Kyle E, et al. Is it possible to promote placental transfusion at preterm delivery? Pediatr Res 1998;44:453.

5. Wardrop CAJ, Holland BM. The roles and vital importance of placental blood to the newborn infant. J Perinat Med 1995;23:139-43.

6. Buckels LJ, Usher R. Cardiopulmonary effects of placental transfusion. J Pediatr 1965;67:239-46.

7. Rabe H, Wacker A, Hulskamp G, Homig-Franz I, Jorch G. Late cord clamping benefits extrauterine adaptation. Pediatr Res 1998;44:454.

8. Mercer J, McGrath M, Hensman A, Silver H, Oh W. Immediate and delayed cord clamping in infants born between 24 and 32 weeks: a pilot randomized controlled trial. J Perinatol 2003;23(6):466-72.

9. Pietra GG, D'Amodio MD, Leventhal MM, Oh W, Braudo JL. Electron microscopy of cutaneous capillaries of newborn infants: effects of placental transfusion. Pediatrics 1968;42(4):678-83.

10. Nelle M, Fischer S, Conze S, Beedgen B, Brischke EM, Linderkamp O. Effects of later cord clamping on circulation in prematures (Abstract). Pediatr Res 1998;44:420.

11. Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database Syst Rev 2004(4):CD003248.

12. Ibrahim H, Krouskop R, Lewis D, Dhanireddy R. Placental transfusion: umbilical cord clamping and preterm infants. J Perinat 2000;20:351-54.

13. Oh W, Carlo W, Fanaroff AA, McDonald S, Donovan EF, Poole K, et al. Delayed cord clamping in extremely low birth weight infants - a pilot randomized controlled trial. Pediatr Res 2002;51(4 Suppl):365-6.

14. Rabe H, Wacker A, Hulskamp G, et al. A randomised controlled trial of delayed cord clamping in very low birth weight preterm infants. Eur J Pediatr 2000;159(10):775-7.

15. McDonnell M, Henderson-Smart DJ. Delayed umbilical cord clamping in preterm infants: a feasibility study. J Paediatr Child Health 1997;33:308-10.

16. Kinmond S, Aitchison TC, Holland BM, Jones JG, Turner TL, Wardrop CA. Umbilical cord clamping and preterm infants: a randomized trial. BMJ 1993;306:172-5.

17. Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ. Periventricular/intraventricular haemorrhage and umbilical cord clamping. Findings and hypothesis. S Afr Med J 1988;73(2):104-6.

18. Hofmeyr GJ, Gobetz L, Bex PJ, et al. Periventricular/intraventricular hemorrhage following early and delayed umbilical cord clamping. A randomized controlled trial. Online J Curr Clin Trials 1993;Doc No 110.

19. Bell MJ. Perforation of the gastrointestinal tract and peritonitis in the neonate. Surg Gynecol Obstet 1985;160(1):20-6.

20. Linderkamp OL. Placental transfusion: determinants and effects. Clin Perinatol 1982;9:599.

21. Stembera ZK, Hodr J, Janda J. Umbilical Blood Flow in Healthy Newborn Infants During the First Minutes after Birth. Am J Obstet Gynecol 1965;91:568-74.

22. Nelle M, Zilow EP, Bastert G, Linderkamp O. Effect of Leboyer childbirth on cardiac output, cerebral and gastrointestinal blood flow velocities in full-term neonates. Am J Perinatol 1995;12(3):212-6.

23. Papile LA, Rudolph AM, Heymann MA. Autoregulation of cerebral blood flow in the preterm fetal lamb. Pediatr Res 1985;19(2):159-61.

24. Volpe J. Neurology of the Newborn. 4th ed. Philadelphia: Saunders; 2001.

25. Wallgren G, Lind J. Quantitative studies of the human neonatal circulation. IV. Observations on the newborn infants peripheral circulation and plasma expansion during moderate hypovolemia. Acta Paediatr Scand 1967:Suppl 179:57+.

26. Yao AC, Lind J. Effect of gravity on placental transfusion. Lancet 1969;2(7619):505-8.

27. Meek JH, Tyszczuk L, Elwell CE, Wyatt JS. Low cerebral blood flow is a risk factor for severe intraventricular haemorrhage. Arch Dis Child Fetal Neonatal Ed 1999;81(1):F15-8.

28. Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. Pediatrics 2003;112(1 Pt 1):33-9.

29. Vohr BR, Allan WC, Westerveld M, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics 2003;111(4 Pt 1):e340-6.

30. van de Bor M, den Ouden, L. School Performance in adolescents with and without periventricular-intraventricular hemorrhage in the neonatal period. Semin Perinatol 2004;24(4):295-303.

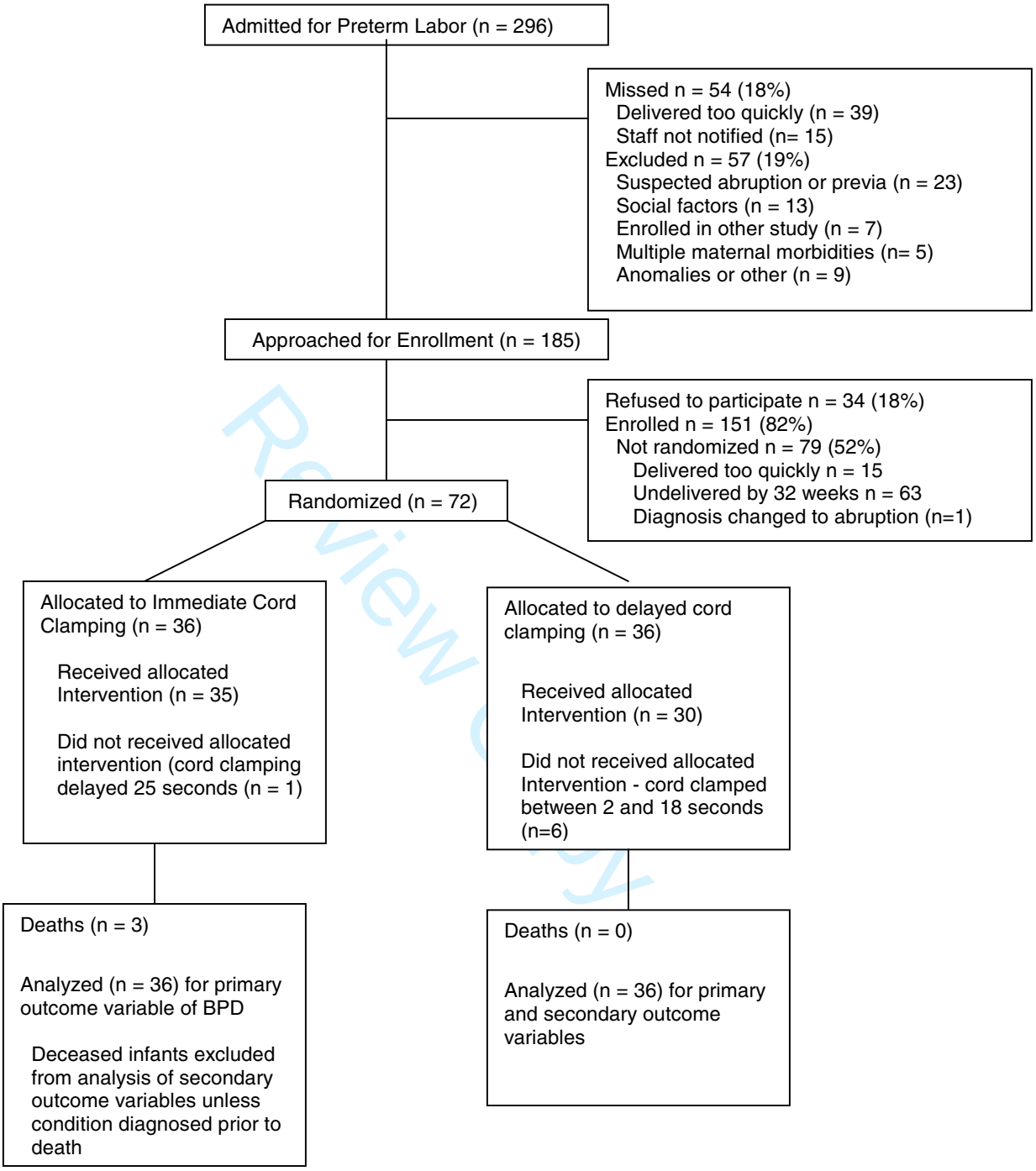
31. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics 1994;93(4):543-50.

32. Stoll, BJ, Hansen NI, et al. Neurodevelopmental and growth impairment among extremely low birth weight infants with neonatal infection. JAMA 2004;292(19):2357-65.

33. Haneline LS, Marshall KP, Clapp DW. The highest concentration of primitive hematopoietic progenitor cells in cord blood is found in extremely premature infants. Pediatr Res 1996;39(5):820-5.

34. Ment, LR, Vohr BR, Makuch RW, Westerveld M, Katz KH, Schneider KC, et al. Prevention of intraventricular hemorrhage in male preterm infants. J. Pediatr 2004;145(6):832-834.

Figure 1.



Legend for Figure 1.

Flow of women admitted for preterm labor between August 2003 and November 2004 including participants in Cord Clamping Study

Table I.

Maternal Demographics, Clinical Characteristics, and Prenatal Medical Management

Characteristics	ICC (n =36)	DCC (n =36)
Mother's Age (yrs) mean + SD	26.8 ± 6.5*	27.1 ± 6.7
Primiparas	25 (69)	23 (64)
Race		
Black	4 (11)	5 (14)
White	20 (56)	18 (50)
Hispanic	11 (30)	11 (31)
Other	1 (3)	2 (6)
Public Insurance	17 (47)	15 (42)
Received Antenatal Steroids	36 (100)	36 (100)
Received Antenatal $MgSO_4$ in 24 hrs before birth	21 (58)	14 (39)
PROM in hours	40 ± 44*	41 ± 47
Cesarean Section	14 (39)	15 (43)
Reasons for Preterm Birth**		
PROM	19 (53)	18 (50)
Preterm Labor	19 (53)	16 (44)
Presumed Chorioamnionitis	10 (28)	11 (31)
Incompetent Cervix	5 (14)	7 (19)
PIH	5 (14)	5 (14)

*Mean + SD. ( ) = %. None of the differences are statistically significant.

**Some mothers had more than one condition.

Table II. Neonatal Demographic , Clinical and Safety Variables

	ICC (n =36)	DCC (n =36)	P Value
Birth weight, g*	1151 ± 379	1175 ± 346	n.s.
Gestational age (weeks)	28.2 ± 2.4	28.3 ± 2.1	n.s.
24 to 27^6 weeks (No.)	15	14	
28 to 31^6 weeks (No.)	21	22	
Male/Female ratio	19/17	23/13	n.s.
Apgar Score Median			
1 min	7 (1-9)	7 (1-9)	n.s.
5 min	8 (1-9)	8 (2-9)	
Temperature on admission to	96.8^O ± 1.5^O	97.1^O ± 1.2^O	n.s.
NICU, ^{O}Farenheit, (range)	(92.8^O – 99.3^O)	(94^O – 99.4^O)	
^{0}Celcius, (range)	36^O ± 0.8^O	36.2^O ± 6^O	
	(33.8^O – 37.4^O)	(34.4^O – 37.4^O)	
Maximum serum Bilirubin (mg/dl)	9.5 ± 2.10	10.1 ± 2.4	n.s.
(Range)	(5.5-13.8)	(6.6-15.1)	
Initial Hematocrit (%)	46 ± 6	49 ± 6	.06
	(34 – 60)	(37 - 62)	
Mean of 1^{st} 4 hrs Mean Blood	31.9 ± 6	33.8 ± 4.5	n.s.
Pressure			
SNAP™ Scores	13.3 ± 12	12.3 ± 11	n.s.
Cord Clamp Time (sec)	6.9 ± 4.3	32.1 ± 12.6	<.001
	(1-25)	(2-49)	
	(median = 5)	(median = 33)	

*Mean ± SD, (range), n.s. = non significant

Table III. Neonatal Morbidities, Blood Loss and Transfusions

	ICC (n = 36)	DCC (n = 36)
	n (%)	n (%)
Death or BPD (O_2 therapy @ 36 weeks)	9 (25)	8 (22)
*Discharge on O_2	4 (12)	5 (14)
Suspected NEC	20 (56)	14 (39)
NEC, Bell[19] Stage		
No sign	25 (69)	27 (75)
1a	7	6
1b	0	2
2a	1	1
3b	2	0
Perforation	1	0
Blood Loss – Week 1, mL	11.4 $\pm$ 5.8	11.3 $\pm$ 5.7
# of Infants Transfused	22 (61)	18 (50)
# of Transfusions	2.47 $\pm$ 3.7	1.94 $\pm$ 3.1
Total Amount Transfused, mL	33 $\pm$ 45	27 $\pm$ 42
*ROP (all)	13 (40)	10 (28)
Deaths	3 (8)	0

*= n of 33 for ICC group as 3 infants in the ICC died before 1 month of age.

None of the differences are statistically significant.

Table IV. IVH and LOS in study infants

	ICC (n = 36)	DCC (n = 36)	p Value	Odds Ratio	95% CI
IVH					
All IVH	13 (36%)	5 (14%)	0.03	3.5	1.1 to 11
Grade 1	4 (11%)	3 (8%)			
Grade 2	8 (22%)	2 (6%)			
Grade 4	1 (3%)	0 (0%)			
Sepsis	8 (22%)	1 (3%)	0.03	.01	0.01 to 0.84

Table V. Gender differences in IVH, LOS, and NEC among infants with ICC and DCC.

	ICC		DCC	
	Boys (n = 19)	Girls (n = 17)	Boys (n = 23)	Girls (n = 13)
IVH	8 (42%)*	5 (29%)	2 (9%)	3 (23%)
Sepsis	6 (32%)*	2 (12%)	0	1 (8%)
NEC	3 (16%)*	1 (6%)	0	2 (15%)

*Differences for boys between groups, $p < .05$, Fisher's Exact Test.