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Authors

Kumbhat, Neha
Eggleston, Barry
Davis, Alexis S
et al.

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Placental Transfusion and Short-Term Outcomes among Extremely Preterm Infants.

Neha Kumbhat, MD, MS Epi[1,2], **Barry Eggleston, MS**[3], **Alexis S. Davis, MD, MS Epi**[1], **Krisa P. Van Meurs, MD**[1], **Sara B. DeMauro, MD, MSCE**[4], **Elizabeth E. Foglia, MD, MSCE**[4], **Satyan Lakshminrusimha, MD**[5], **Michele C. Walsh, MD MS Epi**[6], **Kristi L. Watterberg, MD**[7], **Myra H. Wyckoff, MD**[8], **Abhik Das, PhD**[3], **Sara C. Handley, MD, MSCE**[4,9] **Generic Database Subcommittee of the NICHD Neonatal Research Network**

[1]Stanford University, Stanford, CA

[2]Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA

[3]RTI International, Research Triangle Park, NC

[4]Children's Hospital of Philadelphia, Philadelphia, PA

[5]University of California, Davis, Sacramento, CA

[6]University Hospitals Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, OH

[7]University of New Mexico Health Sciences Center, Albuquerque, NM

[8]University of Texas, Southwestern Medical Center, Dallas, TX

[9]Leonard Davis Institute of Health Economics, The University of Pennsylvania, Philadelphia, PA

Abstract

Objective: To compare short-term outcomes after placental transfusion [delayed cord clamping (DCC) or umbilical cord milking (UCM)] versus immediate cord clamping (ICC) among extremely preterm infants.

Design: Retrospective study.

Corresponding author: Sara C. Handley, MD, MSCE, The Children's Hospital of Philadelphia, Roberts Center for Pediatric Research, Room 19362, 2716 South Street, Philadelphia, PA 19146, Phone: 267-455-5280, Fax: 267-425-0758, handleys@email.chop.edu.

Contributorship statement: NK, AD, KVM, SD and SH designed the project and the main conceptual ideas. BE completed the data analysis. NK, BE, AD, KVM, SD, EF, SL, MW, KW, MW, AD and SH interpreted the analysis. NK and SH drafted the article, which was critically revised by AD, KVM, SD, EF, SL, MW, KW, MW and AD. National Institute of Child Health and Human Development, Eunice Kennedy Shriver provided the Generic Database for this study. NK, BE, AD, KVM, SD, EF, SL, MW, KW, MW, AD, SH and the Generic Database subcommittee gave the final approval to the version submitted for publication.

Research Ethics Approval: This study was performed utilizing the Neonatal Research Network (NRN) Generic Database (GDB) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Institutional review board approval for the NRN GDB registry was obtained for each center.

ClinicalTrials.gov **ID**: Generic Database: NCT00063063

Data Sharing: Data reported in this paper may be requested through a data use agreement. Further details are available at https://neonatal.rti.org/index.cfm?fuseaction=DataRequest.Home.

Setting: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network registry.

Patients: Infants born <29 weeks' gestation in 2016 or 2017 without congenital anomalies who received active treatment after delivery.

Intervention/Exposure: DCC or UCM.

Main Outcome Measures: Primary outcomes: 1) composite of mortality or major morbidity by 36 weeks postmenstrual age (PMA); 2) mortality by 36 weeks PMA; and 3) composite of major morbidities by 36 weeks PMA. Secondary composite outcomes: 1) any grade intraventricular hemorrhage or mortality by 36 weeks PMA; and 2) hypotension treatment in the first 24 postnatal hours or mortality in the first 12 postnatal hours. Outcomes were assessed using multivariable regression, adjusting for mortality risk factors identified a priori, significant confounders, and center as a random effect.

Results: Among 3116 infants, 40% were exposed to placental transfusion, which was not associated with the primary composite outcome of mortality or major morbidity by 36 weeks PMA (aOR 1.26, 95% CI 0.95 to 1.66). However, exposure was associated with decreased mortality by 36 weeks PMA (aOR 0.71, 95% CI 0.55 to 0.92) and decreased hypotension treatment in first 24 postnatal hours (aOR 0.66, 95% CI 0.53 to 0.82).

Conclusion: In this extremely preterm infant cohort, exposure to placental transfusion was not associated with the composite outcome of mortality or major morbidity, though there was a reduction in mortality by 36 weeks PMA.

Keywords

Delayed cord clamping (DCC); umbilical cord milking (UCM); Immediate cord clamping (ICC); Neonatal Research Network (NRN); Generic Database (GDB)

Introduction

Transfer of placental blood to an infant immediately after birth can be achieved through two methods: delayed cord clamping (DCC) or umbilical cord milking (UCM). The American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics (AAP) and the International Liaison Committee on Resuscitation (ILCOR) endorse DCC for 30 to 60 seconds in preterm infants who do not require resuscitation.[1][2][3] The 2015 ILCOR statement recommended against UCM for infants <28 weeks gestational age (GA) as there was no difference in mortality, low quality evidence for intraventricular hemorrhage (IVH) reduction, and limited long term outcome data.[3][4][5][6][7] A meta-analysis of placental transfusion published in 2019, reported that DCC reduced mortality, all grades of IVH, and bronchopulmonary dysplasia (BPD); however, conclusions regarding UCM could not be made due to insufficient data. [8] Randomized controlled trials (RCT) of DCC and UCM continue to emerge with varied results.[9][10] Despite current recommendations, the literature has shown that both methods of placental transfusion are used in clinical practice. [11]

Protocol non-adherence in combination with intent-to-treat analyses may affect findings of placental transfusion RCTs.[12][13][14] Furthermore, infants born <24 weeks GA and of multiple gestation pregnancies are often excluded from RCTs. The Australian Placental Transfusion Study (APTS) recruited infants of multiple gestation pregnancies, however, they were not analyzed separately.[15] The risk-benefit profile in these populations is currently unclear. Documenting outcomes after exposure to placental transfusion in clinical practice, outside of the RCT environment, adds valuable information regarding associations between placental transfusion and outcomes.

This observational study examined the risk-adjusted outcomes, specifically mortality or severe morbidity by 36 weeks postmenstrual age (PMA), after DCC or UCM versus immediate cord clamping (ICC) among infants <29 weeks GA born in Neonatal Research Network (NRN) centers in 2016 and 2017. The study also included two pre-specified exploratory subgroup analyses, infants born <24 weeks GA and infants of twin gestation pregnancies.

Methods

Patient selection

This is a retrospective analysis of prospectively collected data of infants $22^{0/7}$–$28^{6/7}$ weeks GA born in a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development NRN center from 1/1/2016 to 12/31/2017. The NRN Generic Database (GDB) started collecting placental transfusion data on 1/1/2016. Institutional review board approval for the NRN GDB registry was obtained for each center. Infants with missing exposure documentation (N=2), those with severe congenital malformations, including congenital heart disease and/or genetic syndromes, and those who did not receive active treatment after delivery, as previously defined [16], were excluded. Higher order multiples and twins with discordant exposure were eliminated from the twin subgroup analysis, due to infrequency of the former and to ensure analysis within the same exposure group.

Definitions

The NRN GDB collects data from birth until death, hospital discharge, or 120 days of postnatal age using pre-specified definitions.[17][18] Gestational age was determined by best obstetric estimate based on ultrasonography and/or the date of the last menstrual period. Antenatal steroid (ANS) exposure was defined as the administration of at least one dose of dexamethasone or betamethasone during the present pregnancy. Small for gestational age (SGA) was defined as birth weight less than the 10^{th} percentile for sex and GA.[19] Early death was defined as death in the first 12 postnatal hours. Severe brain injury was defined as the presence of severe IVH (grade III or IV), cPVL (cystic periventricular leukomalacia - the presence of cystic echolucencies in the periventricular white matter), porencephalic cyst or ventriculomegaly (the presence of enlarged ventricles) diagnosed on cranial ultrasound obtained closest to 36 weeks PMA.[20] Hypotension treatment was defined as receipt of volume, inotropes, steroids, or a combination thereof in the first 24 postnatal hours. Death in the first 12 postnatal hours precludes collection of hypotension treatment data, thus a composite outcome of hypotension treatment in first 24 hours or mortality in first 12

postnatal hours was used. Late onset sepsis (≥72 postnatal hours) was defined by positive blood culture for bacteria or fungi, and antibiotic therapy for greater than or equal to five days or intent to treat but death occurring before five days.[21] Necrotizing enterocolitis (NEC) was defined as modified Bells stage IIA or greater.[22] Severe retinopathy of prematurity (ROP) was defined as stage 4 disease or greater with 'plus' disease or ROP receiving treatment.[23][24] Bronchopulmonary dysplasia (BPD) was defined as receiving supplemental oxygen or assisted ventilation with or without supplemental oxygen at 36 weeks PMA.[25]

Exposure

Exposure to DCC or UCM was defined using two yes/no questions; 1) Is there documentation of at least 30 seconds of delayed cord clamping? and 2) Is there documentation of cord milking? Infants with 'no' documented exposure to DCC or UCM were classified as exposed to ICC, functionally defined as cord clamping <30 seconds after delivery.

Outcomes

The primary outcomes for this study were informed by the largest trial of DCC–the APTS trial. [15] The primary outcomes were: 1) a composite outcome of death or major morbidity by 36 weeks PMA, with major morbidity defined as any one of severe brain injury, NEC, late onset sepsis, BPD, or severe ROP; 2) death by 36 weeks PMA; and 3) any major morbidity by 36 weeks PMA. Secondary outcomes were: 1) a composite outcome of any grade IVH or mortality by 36 weeks PMA; 2) a composite outcome of hypotension treatment in the first 24 postnatal hours or mortality in the first 12 postnatal hours.

Statistical analysis

Analyses were performed by the NRN Data Coordinating Center (RTI International) using the R statistical software version 3.5.1. Statistical significance was $p < 0.05$. Missingness of the outcome variables was <1% which was handled using complete case analysis while data for which missingness was ≥10% (admission temperature, surfactant, and indomethacin) were excluded from the regression analysis. Baseline characteristics were compared between infants exposed to DCC or UCM versus ICC using *t*-tests for continuous variables and Fisher's exact test for categorical variables. The risk-adjusted association of DCC or UCM with outcomes was assessed using multivariable logistic regression.

Variables in the final model were: 1) mortality risk factors identified *a priori*: sex, GA (in days), ANS exposure, and birth resuscitation (positive pressure ventilation, delivery room intubation, chest compressions and/or epinephrine administration); [18][26][27] 2) covariates that were significantly imbalanced between the groups: race (white/black), maternal insurance, limited prenatal care, maternal magnesium exposure, antenatal hemorrhage, gestational hypertension, mode of delivery, and 5 minute Apgar score ≤4; and 3) NRN center as a random effect. To account for reported associations between birth weight and outcomes, SGA was included in the model though it was not imbalanced between groups.

Both subgroup analyses were adjusted for fewer variables (sex, GA, ANS exposure, chest compressions/epinephrine administration and race) due to model convergence issues.

Results

Study population

Of the 3,116 infants who met inclusion criteria, 40% (n=1,246) were exposed to DCC or UCM (Supplemental figure 1). Of these, 72% (n=895) were exposed to DCC, 23% (n=291) to UCM, and 4.8% (n=60) to DCC and UCM. The <24 weeks GA sub-group included 389 infants of whom 32% (n=126) were exposed to DCC or UCM. There were 596 infants of twin gestation with concordant exposure, of which 40% (n=238) were exposed to DCC or UCM.

Rates of ICC, DCC, and UCM varied across centers (Figure 1). The median center rate of DCC or UCM exposure was 44.4% (range 1.5%−72.4%). Several baseline characteristics differed between the groups, including race, ANS exposure, mode of delivery, GA, Apgar score, and advanced delivery room interventions (Table 1). In regard to race/ethnicity, a larger proportion of infants exposed to ICC had black, non-Hispanic mothers (41%), whereas a larger proportion of the infants exposed to DCC or UCM had white, non-Hispanic mothers (45.7%). Center differences in racial case-mix appear to have contributed to the racial differences in placental transfusion exposure (Supplemental figure 2).

Primary and secondary outcomes

In adjusted analyses, placental transfusion was not associated with the composite outcome of death or major morbidity by 36 weeks PMA (aOR 1.26, 95% CI 0.95 to 1.66) (Table 2). However, it was associated with a statistical and clinically significant decreased odds of mortality by 36 weeks PMA (aOR 0.71, 95% CI 0.55 to 0.92) as well as early mortality (aOR 0.43, 95% CI 0.24 to 0.78). Exposure was also associated with a statistically and clinically significant decrease in the composite outcome of hypotension treatment in the first 24 postnatal hours or death in the first 12 postnatal hours (aOR 0.66, 95% CI 0.53 to 0.82) and decreased odds of receiving a blood transfusion (aOR 0.79, 95% CI 0.63 to 1.00). The composite outcomes of major morbidity by 36 weeks PMA and any IVH or mortality by 36 weeks PMA were not statistically significant.

Exploratory analyses:

Among infants <24 weeks GA, there was no association with mortality by 36 weeks PMA (aOR 0.86, 95% CI 0.53 to 1.41), despite a statistically significantly decreased odds of early mortality (aOR 0.31, 95% CI 0.12 to 0.78) (Table 3). Rates of mortality or major morbidity were 100% for both groups, thus the covariate adjusted models for the primary composite outcomes did not converge. Similar to the primary analysis, the exploratory analysis of twins showed a statistically significant decreased odds of mortality by 36 weeks PMA (aOR 0.54, 95% CI 0.30 to 0.97) and no association with the composite outcome of death or major morbidity (aOR 1.56, 95% CI 0.83 to 3.00) (Table 3).

Post-hoc analyses

A survival analysis was completed to better understand if the mortality benefit at 36 weeks PMA was driven by differences in early mortality or mortality later in the hospitalization. The Kaplan-Meier plots revealed continued separation between the exposed and unexposed groups over time, with survival rates differing by 3.7% on day 1, 5.4% on day 45, and 5.8% on day 75 (Supplemental figure 3). The cause of morality for both groups are reported in supplemental table 1.

Based on the interim RCTs published comparing outcomes after DCC or UCM, a post-hoc analysis of associations between exposure to ICC, DCC, or UCM and the primary outcomes was completed. Although the frequency of adverse outcomes was lowest among infants exposed to DCC, the multivariate analysis did not reveal statistically significant associations (Supplemental table 2).

Discussion

This large, contemporary, retrospective study of placental transfusion practices across the NRN provides generalizable information regarding short-term outcomes among extremely premature infants exposed to DCC or UCM in clinical practice, including a potential survival benefit for exposed infants. It also highlights variation in the application of placental transfusion practices across the NRN. Additionally, the exploratory analyses provide insights into the outcomes of infants <24 weeks GA and twins, both of whom represent high-risk and understudied populations who may benefit from placental transfusion.

The principal finding of this study was the statistically significant and clinically relevant decreased odds of mortality for infants exposed to placental transfusion, which is consistent with the APTS trial.[15] The survival analysis illustrated that early mortality did not entirely explain the mortality difference by 36 weeks PMA. Although mortality in extremely preterm infants is multifactorial, it is closely related to gestational age. In these data more periviable infants (<24 weeks GA) were exposed to ICC, which may contribute to the increased mortality in the ICC group by 36 weeks PMA. Another finding was the statistically significant association between placental transfusion and a decreased odds of hypotension treatment or early mortality. Both hypotension and hypotension treatment are associated with adverse short- and long-term outcomes, thus decreasing exposure to hypotension and associated therapies is likely valuable for extremely preterm infants.[28][29]

Despite governing body statements and published literature, this study illustrates variation in the adoption and application of placental transfusion in clinical practice. One frequently reported fear from obstetricians regarding DCC is a delay in resuscitative efforts, especially in the extremely preterm population.[30] This may be the case in our cohort as 32% of infants born at 23 weeks GA were exposed to placental transfusion compared to 44% born at 28 weeks GA.

Currently, placental transfusion is not recommended for non-vigorous infants and therefore is more likely to be offered to those who are stable at birth.[1][2][3] This leads to a risk of

confounding by indication, as vigorous infants, especially those who do not require advanced delivery room resuscitation, have better outcomes irrespective of placental transfusion.[26][27] This limitation will be addressed by ongoing placental transfusion RCTs that include non-vigorous infants (e.g. VentFirst NCT02742454, Nep-Cord 3 NCT02727517, Baby DUCC Australian Trial Registry 1261800621213).

Studies have suggested that placental transfusion is feasible in multiple gestation pregnancies, including the APTS trial in which 25% of the patients were of twin gestation pregnancies, though reporting of outcomes specific to this population are limited.[15] In this study, 19% of the cohort were twins and those exposed to placental transfusion had a statistically lower odds of mortality, which provides more generalizable data than previously published single center studies.[31][32][33][34] Future analyses of placental transfusion involving twins should consider other contributing factors, specifically chorionicity and birth order, which were not captured in this analysis. The statistically significant association between placental transfusion and early mortality in infants <24 weeks GA suggests that placental transfusion either confers an immediate benefit or that sicker infants received ICC. Placental transfusion does not mitigate adverse outcomes in this population, as 100% of infants <24 weeks GA either died or experienced a major morbidity, the most common of which was BPD, that influenced the high composite outcomes.[35]

This study has several limitations. Retrospective studies are susceptible to covariate imbalances of unmeasured factors. The placental transfusion group had more favorable baseline characteristics (e.g. more ANS and magnesium sulfate exposure, less antenatal hemorrhage, higher Apgar scores, and less resuscitation interventions) and despite model adjustments this could influence study findings. Thus, the apparent benefits of placental transfusion should be interpreted with caution and verified in other populations. In this study, both placental transfusion techniques were combined to improve the study power. Given that 70% of the exposed infants were exposed to DCC, the study findings overrepresent DCC associated outcomes and do not allow for generalization of findings to DCC or UCM alone. The interim publications motivated our post-hoc analysis comparing ICC, DCC, and UCM, which did not detect statistical differences in the primary outcomes, however the current study was not powered for this analysis.[10][36] The GA-associated effects of UCM reported by Katheria et al. and our post-hoc analysis emphasis the ongoing need for studies with sufficient power to compare the effects of DCC versus UCM.[37][38] Although the GDB prospectively collects DCC and UCM data, documentation errors may result in exposure misclassification, as was illustrated by a study using delivery room video recordings.[39] The lack of granular data regarding placental transfusion is another limitation. For example, the duration of DCC, the number of times the cord was stripped/milked in UCM, or the timing of placental transfusion in relation to onset of breathing are not known. Additionally, data are not collected regarding the obstetric or neonatal considerations that may influence practitioners to forgo placental transfusion. Finally, while large databases highlight variation in clinical practice (e.g. implementation of placental transfusion, indomethacin use for IVH prevention or patent ductus arteriosus treatment) such variation may exaggerate or mask study findings.

This study is one of the largest, multisite, observational cohort studies examining placental transfusion and outcomes in extremely preterm infants and highlights variation in placental transfusion practices across the NRN. These findings add to the literature from large databases, such as the California Perinatal Quality Care Collaborative and Canadian Neonatal Network, supporting placental transfusion.[11][40] Specific strengths of this study include the reporting of associated outcomes and contemporary data as placental transfusion practices have evolved. Notably, previous studies of this size have not reported the outcomes of twins or infants <24 weeks GA. Although our analysis was not powered for these subgroups, there was no evidence of harm and instead some suggestion of clinical benefit in twins. These results are hypothesis-generating and may provide data for future RCTs.

Summary

In conclusion, this large observational study of infants <29 weeks GA, did not find an association between placental transfusion and the composite outcome of mortality or major morbidity; however, there was a statistically significant decrease in mortality and hypotension treatment. The application of placental transfusion outside of clinical trials is associated with clinical benefits for extremely preterm infants, which may extend to twins.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Participating NRN sites collected data and transmitted it 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, RTI International had full access to all of the data in the study, and with the NRN Center Principal Investigators, takes responsibility for the integrity of the data and accuracy of the data analysis.

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Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (UG1 HD27904) – Abbot R. Laptook, MD; Martin Keszler, MD; Angelita M. Hensman, PhD RNC-NIC; Elisa Vieira, BSN RN; Lucille St. Pierre, BS.

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University of Alabama at Birmingham Health System and Children's Hospital of Alabama (UG1 HD34216) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN.

University of California - Los Angeles, Mattel Children's Hospital, Santa Monica Hospital, Los Robles Hospital and Medical Center, and Olive View Medical Center (U10 HD68270) – Uday Devaskar, MD; Meena Garg, MD; Teresa Chanlaw, MPH; Rachel Geller, RN BSN.

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University of Pennsylvania, Hospital of the University of Pennsylvania, Pennsylvania Hospital, and Children's Hospital of Philadelphia (UG1 HD68244) – Eric C. Eichenwald, MD; Barbara Schmidt, MD MSc; Haresh Kirpalani, MB MSc; Aasma S. Chaudhary, BS RRT; Soraya Abbasi, MD; Toni Mancini, RN BSN CCRC; Sarvin Ghavam, MD; Jonathan Snyder, RN BSN; Christine Catts, CRNP.

University of Rochester Medical Center, Golisano Children's Hospital, and the University at Buffalo John R. Oishei Children's Hospital of Buffalo (UG1 HD68263, UL1 TR42) – Carl T. D'Angio, MD; Ronnie Guillet, MD PhD; Anne Marie Reynolds, MD MPH; Satyan Lakshminrusimha, MD; Holly I.M. Wadkins, MA; Michael G. Sacilowski, MAT CCRC; Mary Rowan, RN; Rosemary Jensen; Dee Maffett, RN; Diane Prinzing, AAS; Ann Marie Scorsone, MS CCRC; Kyle Binion, BS; Stephanie Guilford, BS; Constance Orme; Premini Sabaratnam, MPH; Daisy Rochez, BS MHA.

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References:

1. Delayed umbilical cord clamping after birth. Committee Opinion No. 684. American College of Obstetricians and Gynecologists. Obstetrics Gynecology 2017;129: e5–10. [PubMed: 28002310]
2. Timing of umbilical cord clamping after birth. Pediatrics 4 2013;131: e1323–e1323.
3. Perlman JM, Wyllie J, Kattwinkel J, et al. Part 7: Neonatal Resuscitation: 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations (Reprint). Pediatrics 2015;136: S120–66. [PubMed: 26471381]
4. Al-Wassia H, Shah PS. Efficacy and safety of umbilical cord milking at birth: A systematic review and meta-analysis. JAMA Pediatrics 2015; 169:18. [PubMed: 25365246]
5. Nagano N, Saito M, Sugiura T, et al. Benefits of umbilical cord milking versus delayed cord clamping on neonatal outcomes in preterm infants: A systematic review and meta-analysis. PLoS ONE 2018;13: e0201528. [PubMed: 30161139]
6. Katheria A, Garey D, Truong G, et al. A randomized clinical trial of umbilical cord milking vs delayed cord clamping in preterm infants: Neurodevelopmental outcomes at 22–26 months of corrected age. The Journal of Pediatrics 2018; 194:76–80. [PubMed: 29246467]
7. Rabe H, Sawyer A, Amess P, et al. Neurodevelopmental outcomes at 2 and 3.5 years for very preterm babies enrolled in a Randomized trial of milking the umbilical cord versus delayed cord clamping. Neonatology 2016; 109:113–9. [PubMed: 26650133]
8. Rabe H, Gyte GM, Díaz-Rossello JL, 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 of Systematic Reviews Published online first: 17 September 2019.
9. Shirk SK, Manolis SA, Lambers DS, et al. Delayed clamping vs milking of umbilical cord in preterm infants: a randomized controlled trial. American Journal of Obstetrics & Gynecology 2019; 220:482. e1–482.e8. [PubMed: 30786254]
10. Katheria A, Reister F, Essers J, et al. Association of umbilical cord milking vs delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm infants. JAMA 2019; 322:1877. [PubMed: 31742630]
11. Tran C, Parucha J, Jegatheesan P, et al. Delayed cord clamping and umbilical cord milking among infants in California neonatal intensive care units. American Journal of Perinatology 2019: s-0039–1683876.
12. Ibrahim HM, Krouskop RW, Lewis DF, et al. Placental transfusion: Umbilical cord clamping and preterm infants. Journal of Perinatology:2000: s20,351–354
13. Sommers R, Stonestreet BS, Oh W, et al. Hemodynamic effects of delayed cord clamping in premature infants. Pediatrics 2012;129: e667–72. [PubMed: 22331336]
14. Kugelman A, Borenstein-Levin L, Riskin A, et al. Immediate versus delayed umbilical cord clamping in premature neonates born < 35 weeks: A prospective, randomized, controlled study. American Journal of Perinatology 2007; 24:307–15. [PubMed: 17516307]
15. Tarnow-Mordi W, Morris J, Kirby A, et al. Delayed versus immediate cord clamping in preterm infants. N Engl J Med 2017; 377:2445–55. [PubMed: 29081267]
16. Rysavy MA, Li L, Bell EF, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. New England Journal of Medicine 2015; 372:1801–11.

17. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. American Journal of Obstetrics and Gynecology 2007; 196:147. e1–147.e8. [PubMed: 17306659]
18. Eunice Kennedy Shriver NICHD Neonatal Research Network. Survey of morbidity and mortality among high risk preterm infants (GDB). Manual of operations. 2017
19. Alexander G, Himes J, Kaufman R, et al. A united states national reference for fetal growth. Obstetrics & Gynecology 1996; 87:163–8. [PubMed: 8559516]
20. Papile L-A, 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. The Journal of Pediatrics 1978; 92:529–34. [PubMed: 305471]
21. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. Pediatrics 2002; 110:285–91. [PubMed: 12165580]
22. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978; 187:17. [PubMed: 619796]
23. Early treatment for retinopathy of prematurity cooperative group et al. Multicenter trial of early treatment for retinopathy of prematurity: study design. Controlled Clinical Trials 2004; 25:311–25. [PubMed: 15157731]
24. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmology 2003; 121:13.
25. Shennan AT, Dunn MS, Ohlsson A, et al. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988; 82:527. [PubMed: 3174313]
26. Wyckoff MH, Salhab WA, Heyne RJ, et al. Outcome of extremely low birth weight infants who received delivery room cardiopulmonary resuscitation. The Journal of Pediatrics 2012; 160:239–244.e2. [PubMed: 21930284]
27. Handley SC, Sun Y, Wyckoff MH, et al. Outcomes of extremely preterm infants after delivery room cardiopulmonary resuscitation in a population-based cohort. J Perinatology 2015; 35:379–83.
28. Kuint J, Barak M, Morag I, et al. Early Treated Hypotension and Outcome in Very Low Birth Weight Infants. Neonatology 2009; 95:311–6. [PubMed: 19052477]
29. Batton B, Li L, Newman NS for the Eunice Kennedy Shriver National Institute of Child Health & Human Development Neonatal Research Network, et al. Early blood pressure, antihypotensive therapy and outcomes at 18–22 months' corrected age in extremely preterm infants. Archives of Disease in Childhood - Fetal and Neonatal Edition 2016;101: F201–F206. [PubMed: 26567120]
30. Jelin AC, Kuppermann M, Erickson K, et al. Obstetricians' attitudes and beliefs regarding umbilical cord clamping. The Journal of Maternal-Fetal & Neonatal Medicine 2014; 27:1457–61. [PubMed: 24215582]
31. Chiruvolu A, Daoud Y, Inzer RW. Effect of delayed cord clamping on very preterm twins. Early Human Development 2018; 124:22–5. [PubMed: 30099274]
32. Ruangkit C, Leon M, Hassen K, et al. Maternal bleeding complications following early versus delayed umbilical cord clamping in multiple pregnancies. BMC Pregnancy Childbirth 2018; 18:131. [PubMed: 29728153]
33. Jegatheesan P, Belogolovsky E, Nudelman M, et al. Neonatal outcomes in preterm multiples receiving delayed cord clamping. Arch Dis Child Fetal Neonatal Ed 2019;104: F575–81. [PubMed: 30894397]
34. Rodriguez C, Metz T, Patel S, et al. Neonatal outcomes associated with umbilical cord milking in preterm multiple gestations. Amer J Perinatology 2019; s-0039–1679915.
35. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA 2015; 314:1039. [PubMed: 26348753]
36. Rabe H, Andersson O. Maternal and infant outcomes after different methods of umbilical cord management. JAMA 2019; 322:1864. [PubMed: 31742617]

37. Shirk SK, Manolis SA, Lambers DS, et al. Delayed clamping vs milking of umbilical cord in preterm infants: a randomized controlled trial. American Journal of Obstetrics and Gynecology 2019; 220:482. e1–482.e8. [PubMed: 30786254]

38. Ram Mohan G, Shashidhar A, Chandrakala BS, et al. Umbilical cord milking in preterm neonates requiring resuscitation: A randomized controlled trial. Resuscitation 2018; 130:88–91. [PubMed: 29981817]

39. Fishman CE, Weinberg DD, Murray A, et al. Accuracy of real-time delivery room resuscitation documentation Archives of Disease in Childhood - Fetal and Neonatal Edition 2020;105:222–224. [PubMed: 30472661]

40. Lodha A, Shah PS, Soraisham AS, et al. Association of deferred vs immediate cord clamping with severe neurological injury and survival in extremely low-gestational-age neonates. JAMA Network Open 2019;2: e191286. [PubMed: 30924898]

What is already known?

- Both DCC and UCM are effective methods to achieve placental transfusion.
- Current recommendations endorse delayed cord clamping (DCC) in preterm infants who do not require resuscitation.
- Previous literature has suggested inconsistent adoption of placental transfusion in clinical practice.

What is unknown?

- The frequency of exposure to placental transfusion is clinical practice is not well described.
- Short-term outcomes associated with placental transfusion outside of randomized controlled trials have not been well described in the United States.
- Associations between placental transfusion and short-term outcomes in high risk and often understudied populations, specifically infants <24 weeks GA and twins, are unknown.

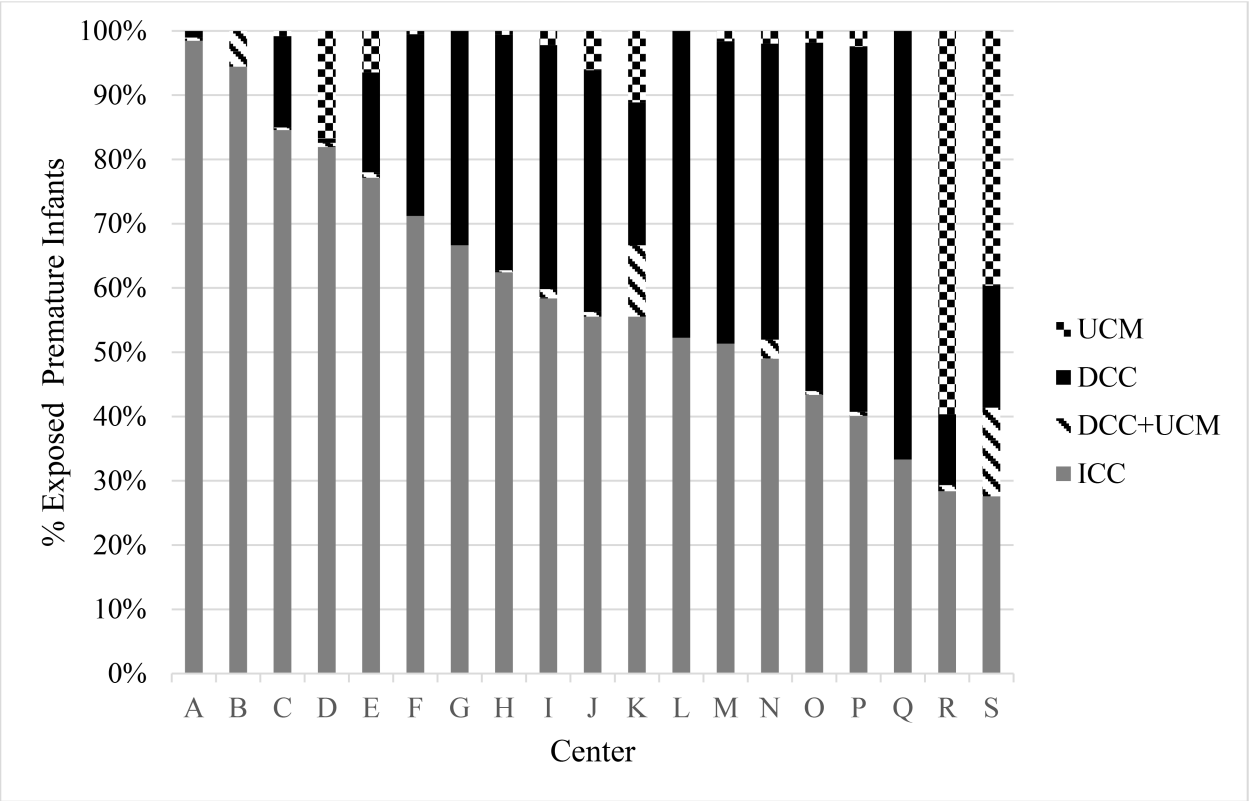

Figure 1: Rates of ICC, DCC, and UCM by NRN center, 2016–2017

ICC = Immediate cord clamping, DCC = Delayed cord clamping, UCM = Umbilical cord milking

Table 1:

Maternal and neonatal characteristics among those exposed to ICC versus those exposed to DCC/UCM

Characteristics	ICC (N = 1870)	DCC/UCM (N = 1246)	p-value*
Maternal characteristics			
Maternal age (years), mean (SD)	28.7 (6.2)	28.5 (5.9)	0.40
Race/Ethnicity			< 0.0001
Black, non-Hispanic	767 (41%)	410 (33%)	
White, non-Hispanic	654 (35%)	568 (46%)	
Hispanic	343 (18.3%)	165 (13.3%)	
Asian	59 (3.2%)	50 (4.0%)	
Other/Unknown/not reported	47 (2.5%)	50 (4%)	
Insurance			<0.0001
Private	574 (36.4%)	574 (46.1%)	
Public	1125 (60.2%)	614 (49.3%)	
Other	64 (3.42%)	57 (4.58%)	
Limited or no prenatal care	265 (14.2%)	126 (10.1%)	< 0.0001
Received antenatal steroids	1684 (90.1%)	1205 (96.9%)	< 0.0001
Antenatal MgSo4	1519 (81.4%)	1135 (91.2%)	< 0.0001
Diabetes prior to pregnancy	85 (4.6%)	50 (4.0%)	0.53
Gestational diabetes	83 (4.5%)	55 (4.4%)	1.00
Hypertension during pregnancy	580 (31%)	352 (28.2%)	0.10
Pregnancy induced hypertension	271 (14.5%)	179 (14.4%)	0.96
Premature rupture of membranes	1014 (54.8%)	640 (52.6%)	0.09
Prolonged rupture of membranes	489 (26.4%)	340 (27.4%)	0.53
Chorioamnionitis	929 (50%)	623 (50%)	0.88
Maternal antibiotics	1429 (76.7%)	1022 (82.1%)	< 0.0001
Antepartum hemorrhage	504 (27.0%)	225 (18.1%)	< 0.0001
Cesarean delivery	1279 (68.4%)	805 (64.5%)	0.03
Neonatal characteristics			
Gestational age (weeks)			0.008
$22^{0/7}$–$22^{6/7}$ weeks	44 (2.4%)	23 (1.9%)	
$23^{0/7}$– $23^{6/7}$ weeks	219 (11.7%)	103 (8.3%)	
$24^{0/7}$ – $24^{6/7}$ weeks	250 (13.4%)	149 (12%)	
$25^{0/7}$ – $25^{6/7}$ weeks	290 (15.5%)	186 (14.9%)	
$26^{0/7}$–$26^{6/7}$ weeks	325 (17.4%)	228 (18.3%)	
$27^{0/7}$–$27^{6/7}$ weeks	345 (18.5%)	240 (19.3%)	
$28^{0/7}$–$28^{6/7}$ weeks	397 (21.2%)	317 (25.4%)	
GA in weeks (continuous), mean (SD)	26.2 (1.8)	26.4 (1.7)	0.0001
Birth weight (grams), mean (SD)	839.2 (250.4)	871.8 (244.5)	0.0001
SGA	177 (9.5%)	106 (8.5%)	0.37
Male	966 (51.7%)	629 (50.5%)	0.53
Multiple gestation	486 (26%)	342 (27.5%)	0.38

Characteristics	**ICC (N = 1870)**	**DCC/UCM (N = 1246)**	**p-value***
Apgar scores			
≤4 at 1 minute	1207 (64.8%)	634 (51.1%)	<0.0001
≤4 at 5 minutes	451(24.2%)	202 (16.2%)	<0.0001
Delivery room interventions			
PPV	1644 (87.9%)	1004 (80.6%)	<0.0001
Intubation	1229 (65.7%)	726 (58.3%)	<0.0001
Chest Compressions	119 (6.4%)	54 (4.3%)	0.02
Epinephrine	64 (3.4%)	30 (2.4%)	0.11
Admission temperature (Celsius)	36.6 (1.2)	36.6 (0.8)	0.006
Hypothermia on admission#	267 (14.6%)	167 (13.5%)	0.43
Surfactant	1414 (79.5%)	927 (75.6%)	0.01
Indomethacin administration in the first 24 hours	572 (32.2%)	293 (23.9%)	<0.0001

ICC = Immediate cord clamping, DCC = Delayed cord clamping, UCM= Umbilical cord milking, SD = Standard deviation, PPV = Positive pressure ventilation, GA=Gestational age, SGA = Small for gestational age. Other insurance included self-pay, uninsured and unknown insurance.

*p-values based on t-test/Wilcoxon rank sum test for continuous variables and Fischer's exact test for categorical variables. Data presented as % for categorical variables and mean (SD) for continuous variables.

#Hypothermia defined as less than 36 degree Celsius.

Table 2:

Neonatal outcomes among infants exposed to ICC versus infants exposed to DCC/UCM

Outcomes	ICC	DCC /UCM	OR	aOR (95% CI)
Primary Outcomes *	**(N = 1870)**	**(N = 1246)**		
Mortality or major morbidity by 36 weeks PMA #	1525 (83.4%)	1039 (85.2%)	1.14 (0.93, 1.39)	1.26 (0.95, 1.66)
Mortality by 36 wks PMA	334 (17.9%)	152 (12.2%)	0.64 (0.64, 0.78)	0.71 (0.55, 0.92)
Major morbidity by 36 weeks PMA #	1313 (81.3%)	958 (84.1%)	1.22 (1.00, 1.49)	1.29 (0.97, 1.70)
Secondary Outcomes				
Any IVH or mortality by 36 wks PMA	759 (40.8%)	454 (36.6%)	0.84 (0.72, 0.97)	0.95 (0.79, 1.13)
Therapy for hypotension in the first 24 hours or mortality in the first 12 hours	502 (26.9%)	293 (23.5%)	0.84 (0.71, 0.99)	0.66 (0.53, 0.82)
Other outcomes				
Death < 12 hours	89 (4.8%)	20 (1.6%)	0.32 (0.20, 0.53)	0.43 (0.24, 0.78)
Other outcomes, restricted to survivors of first 12 hours				
	(N=1780)	**(N=1226)**		
PRBC transfusion	1405 (79.0%)	865 (70.6%)	0.64 (0.54, 0.75)	0.79 (0.63, 1.00)
Time to PRBC transfusion, days	3 (1, 9)	5 (2, 11)	1.00 (−0.08, 2.09)	−0.02 (−1.13, 1.09) ◊
Severe brain injury				
Severe IVH **	264 (15.2%)	168 (14.2%)	0.92 (0.75, 1.13)	1.02 (0.80, 1.31)
Cystic PVL	89 (5.1%)	47 (4.0%)	0.78 (0.54, 1.11)	0.92 (0.63, 1.35)
Porencephalic cyst	27 (1.5%)	20 (1.6%)	1.08 (0.60, 1.93)	1.34 (0.70, 2.55)
Ventriculomegaly	168 (9.5%)	99 (8.1%)	0.84 (0.65, 1.09)	1.03 (0.77, 1.39)
Any IVH	558 (32.1%)	369 (30.9%)	0.94 (0.81, 1.11)	1.02 (0.85, 1.23)
NEC ***	166 (9.4%)	104 (8.5%)	0.90 (0.70, 1.16)	1.01 (0.75, 1.35)
Late onset sepsis †	348 (19.6%)	213 (17.4%)	0.86 (0.72, 1.04)	0.89 (0.72, 1.10)
Other outcomes, restricted to infants surviving at 36 wks PMA ##				
	(N=1534)	**(N=1094)**		
BPD	1155 (76.6%)	862 (79.9%)	1.21 (1.00, 1.47)	1.28 (0.98, 1.67)
Severe ROP ****	147 (9.9%)	87 (8.2%)	0.81 (0.62, 1.07	0.83 (0.58, 1.18)
Length of stay, days	84 (69, 98)	82 (68, 99)	−0.33 (−2.18, 1.52)	0.50 (−1.05, 2.05) ◊

ICC = Immediate cord clamping, DCC = Delayed cord clamping, UCM=Umbilical cord milking, aOR= Adjusted odds ratio, PMA=Post menstrual age, IVH = Intraventricular hemorrhage**, PRBC=Packed red blood cells, PVL=Periventricular leukomalacia, NEC = Necrotizing enterocolitis***, BPD Bronchopulmonary dysplasia (supplemental oxygen or assisted ventilation with or without supplemental oxygen at 36 weeks PMA), ROP = retinopathy of prematurity

* Variables in the model included: sex, GA (in days), SGA, race, antenatal steroids, limited or no prenatal care (defined as less than three visits or care starting in the third trimester), antenatal MgSo4, antenatal hemorrhage (placenta previa, abruption or threatened abortion resulting in bleeding after 20 weeks), hypertension during pregnancy, mode of delivery, delivery room (DR) PPV, DR intubation, DR resuscitation (chest compressions and/or epinephrine), 5 minute Apgar ≤4.

** Severe IVH (grade III or IV)

*** NEC stage II or greater

**** Severe ROP (stage 4 or requiring treatment)

Composite outcome includes death or major morbidity (severe brain injury, NEC, late onset sepsis, BPD, severe ROP)

Data presented as n (%) for categorical variables and median (IQR) for continuous variables.

† Due to convergence issues, covariates included: gender, GA, antenatal steroids, resuscitation (chest compression and/or epinephrine), and race.

Infants discharged prior to 36 weeks PMA were included.

◊ Adjusted mean difference reported for continuous variables

Table 3:

Neonatal outcomes among infants <24 weeks GA or twin gestation exposed to ICC versus those exposed to DCC/UCM

Outcomes	ICC	DCC /UCM	OR	aOR (95% CI)
Outcomes among infants restricted to $22^{0/7}$through $23^{6/7}$				
Primary Outcomes*	**(N = 263)**	**(N = 126)**		
Mortality or major morbidity by 36 wks PMA[#]	263 (100%)	125 (100%)	n/a	n/a
Mortality by 36 wks PMA	127 (48.3%)	55 (43.6%)	0.83, (0.54, 1.27)	0.86 (0.53, 1.41)
Major morbidity by 36 wks PMA[#]	181 (100%)	99 (100%)	n/a	n/a
Secondary Outcomes				
Any IVH or mortality by 36 wks PMA	193 (73.9%)	94 (74.6%)	1.03 (0.64, 1.68)	1.19 (0.68, 2.08)
Therapy for hypotension in the first 24 hours or mortality in the first 12 hours	145 (55.1%)	69 (54.7%)	0.99 (0.64, 1.51)	0.77 (0.46, 1.29)
Other outcomes				
Death <12 hours	44 (16.7%)	7 (5.56%)	0.29 (0.13, 0.67)	0.31 (0.12, 0.78)
Outcomes among infants twin gestation infants with concordant DCC or UCM exposure.				
Primary Outcomes	**(N = 358)**	**(N = 238)**		
Mortality or major morbidity by 36 wks PMA [#]	288 (82.5%)	206 (88.4%)	1.62 (0.99, 2.63)	1.58 (0.83, 3.00)
Mortality by 36 wks PMA	75 (20.9%)	32 (13.4%)	0.59 (0.37, 0.92)	0.54 (0.30, 0.97)
Major morbidity by 36 wks PMA[#]	242 (79.9%)	185 (87.3%)	1.73 (1.06, 2.82)	1.65 (0.87, 3.14)
Secondary outcomes				
Any IVH or mortality by 36 wks PMA	155 (43.4%)	83 (34.9%)	0.70 (0.50, 0.98)	0.70 (0.45, 1.07)
Therapy for hypotension in the first 24 hours or mortality in the first 12 hours	106 (29.6%)	72 (30.3%)	1.03 (0.72, 1.47)	0.57 (0.35, 0.96)
Other outcomes				
Death <12 hours	14 (4%)	5 (2.1%)	0.53 (0.19, 1.48)	0.44(0.11,1.76)

ICC = Immediate cord clamping, DCC = Delayed cord clamping, UCM=Umbilical cord milking, aOR= Adjusted odds ratio, PMA=Post menstrual age, IVH = Intraventricular hemorrhage.

[#]Composite outcome includes death or major morbidity (severe brain injury, NEC, late onset sepsis, BPD, severe ROP)

Data presented as n (%) for categorical variables and median (IQR) for continuous variables.