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Exposure to Umbilical Cord Management Approaches and Death or Neurodevelopmental Impairment at 22–26 Months Corrected Age after Extremely Preterm Birth

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Abstract

Objective: To compare death or severe neurodevelopmental impairment (NDI) at 22–26 months’ corrected age (CA) among extremely preterm infants following exposure to different forms of umbilical cord management.

Design: Retrospective study.

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

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

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.

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

Patients: Infants born <27 weeks' gestation in 2016–2018 without severe congenital anomalies who received active treatment after birth and underwent neurodevelopmental assessments between 22–26 months' CA.

Exposures: Immediate cord clamping (ICC), delayed cord clamping (DCC) or umbilical cord milking (UCM).

Main Outcomes and Measure: Primary composite outcome of death or severe NDI at 22–26 months' CA, defined as severe cerebral palsy, Bayley-III cognitive/motor composite score <70, bilateral deafness or blindness; individual components were examined as secondary outcomes. Multivariable regression examined associations, adjusting for risk factors identified *a priori* and potential confounders. Mediation analysis explored the effect of severe intraventricular hemorrhage (IVH) on the exposure-outcome relationship.

Results: Among 1,900 infants, 64.1% were exposed to ICC, 27.8% to DCC, and 8.1% to UCM. Compared to ICC-exposed infants, DCC-exposed infants had lower odds of death or severe NDI (aOR 0.64, 95% CI 0.50–0.83). No statistically significant differences were observed when comparing UCM with either ICC or DCC, or between secondary outcomes across groups. Association between cord management and the primary outcome was not mediated by severe IVH.

Conclusion: Compared to ICC, DCC exposure was associated with lower death or severe NDI at 22–26 months' CA among extremely preterm infants, which was not mediated by severe IVH.

Keywords

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

Introduction

The prognosis of extremely low birth weight (ELBW) infants surviving to hospital discharge remains guarded, as a large proportion experience neurodevelopmental impairment (NDI).[1]⁻[2] Severe intraventricular hemorrhage (IVH) may contribute to NDI in the ELBW population.[3]⁻[4] Forms of placental transfusion, such as delayed cord clamping (DCC), offer a potential neuro-protective strategy for ELBW infants.[5] Studies evaluating the relationships of DCC, umbilical cord milking (UCM), and immediate cord clamping (ICC) with severe IVH have reported mixed findings, leaving questions about neuroprotection and neurodevelopment unanswered.

Most studies examining umbilical cord management and neurodevelopmental outcomes are limited by small sample size, single center cohorts with heterogenous neurodevelopmental measures, and variable assessment time points. [6] [7] [8] Recent data from the Australian Placental Transfusion Study (APTS) showed a 30% relative risk reduction of death with no difference in major disabilities at two years among DCC-exposed infants, compared to ICC-exposed infants.[9] The International Liaison Committee of Resuscitation systematic review and meta-analysis, published in 2015, recommends DCC following extremely preterm birth, but does not recommend UCM due to low quality evidence and limited long-term outcome data.[10] Evidence about neurodevelopmental outcomes comparing all three approaches to cord management, DCC, ICC, and UCM, remains limited.

We have examined short-term outcomes following different approaches to umbilical cord management among extremely preterm infants and demonstrated that DCC is the preferred approach, as UCM was associated with increases in severe IVH. [11] [12] Using the detailed follow-up data collected by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN), the objective of the current study was to compare rates of death or severe NDI at 22–26 months' corrected age (CA) after exposure to ICC, DCC, or UCM among infants born <27 weeks' gestation. Individual components of the primary composite outcome were examined as secondary outcomes. This study also explored whether the relationship between cord management and the primary outcome was mediated by severe IVH.

Methods

Patient selection

This retrospective analysis included infants $22^{0/7}$ to $26^{6/7}$ weeks' gestation born at NRN centers from January 1st 2016 to December 31st 2018. The NRN Generic Database (GDB) registry collects sociodemographic, maternal, and neonatal information prospectively during the birth hospitalization using previously defined, pre-specified definitions.[12] [13] The Follow-up (FU) database collects neurodevelopmental assessments of eligible survivors born <27 weeks' gestation at 22–26 months' CA. Each participating center obtained institutional review board (IRB) approval for both databases; per local IRB guidance a waiver of consent was approved or parental consent obtained.

Infants with missing exposure documentation, those with severe congenital malformations, including congenital heart disease and/or genetic syndromes, and those who did not receive active treatment after birth (any ventilatory support, chest compressions, epinephrine administration, surfactant, mechanical ventilation, or parental nutrition) were excluded [14]. Infants with neurodevelopmental assessments completed more than four months outside of the target window of 22–26 months CA were excluded. The final cohort included infants who died prior to follow-up and survivors with complete neurodevelopmental assessments. Survivors without NDI data were deemed lost to follow-up. The total number of infants exposed to the three cord management forms was used as a denominator to calculate lost-to-follow-up rates.

Exposures

The exposure was the documented approach to umbilical cord management performed in the delivery room as decided by the clinical team and center practice guidelines. Exposure to DCC, UCM, or ICC was determined using two yes/no questions answered for each infant in the GDB: 1) Is there documentation of at least 30 seconds of DCC? and 2) Is there documentation of UCM? Infants with answers to both questions documented as 'no' were classified as exposed to ICC, functionally defined as cord clamping <30 seconds after birth. Infants with missing data and those with answers to both questions documented as 'yes' were excluded, thus the analytic cohort only includes infants with one documented exposure.

Outcomes

The primary outcome was a composite of death before follow-up evaluation or severe NDI at follow-up (defined below). The neurodevelopmental assessment included a physical examination with standardized neurological examination and developmental evaluation using the Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley-III), administered by certified examiners.[15][16] A score <70 on any of the Bayley-III composite scales indicates development that is two standard deviations below the expected population mean score. The language composite score includes assessment of both receptive and expressive language. Motor abilities were also classified using the Gross Motor Function Classification System (GMFCS) and severity of cerebral palsy (CP) was classified using the GMFCS level: mild (level 1), moderate (level 2–3), and severe CP (level 4–5).[17] Bilateral blindness was defined as vision <20/200 despite corrective lenses bilaterally. Hearing impairment was defined as permanent hearing loss with or without amplification and obtained by parental report. The NRN follow up subcommittee defines severe NDI as the presence of any one of the following: severe CP, Bayley-III cognitive composite score <70, Bayley-III motor composite score <70, bilateral blindness or hearing impairment.[18] Secondary outcomes were: 1) death prior to follow-up evaluation, and among survivors: 2) severe NDI, 3) moderate or severe CP (GMFCS ≥2), 4) severity of CP based on GMFCS level, 5) Bayley-III cognitive score <70, 6) Bayley-III cognitive score <85, 6) Bayley-III motor score <70 7) Bayley-III composite language score <70, 8) bilateral blindness and 9) hearing impairment.

Statistical analysis

We examined three comparisons: DCC versus ICC, UCM versus ICC, and DCC versus UCM. Unadjusted comparisons were made between groups for sociodemographic and perinatal-neonatal characteristics using t-tests and Fischer's exact test for continuous and categorical variables, respectively. Risk-adjusted associations of cord management technique with the primary composite outcome were estimated using complete case analysis and multivariable logistic regression. The regression model incorporated the following variables: 1) risk factors for death or severe NDI identified *a priori:* gestational age (in weeks), sex, race/ethnicity, maternal education, and antenatal steroids; [19] 2) covariates occurring prior to the exposure that were statistically imbalanced across the three exposure groups (p-value ≤ 0.1) in unadjusted analyses; 3) birth year; and 4) NRN center as a random effect. The same model examined secondary outcomes. Models assessing severe NDI among survivors also included age at follow-up assessment. No adjustments were made for multiple comparisons. To examine the effect of the coronavirus 2019 (COVID-19) pandemic on disruptions to healthcare delivery, specifically, the effect on follow-up assessment timing, we performed a sensitivity analysis limiting the study population to infants who reached 26 months' CA by March 15th, 2020.

A prespecified mediation analysis examined whether severe IVH mediated the relationship between cord management and the primary outcome. Given that severe IVH is a binary variable, a model-based causal mediation analysis using differences in proportions was used to report direct and indirect effects of the mediator on the outcome of interest. This analysis quantifies the association between the exposure and the outcome without (direct) and through (indirect) the mediator, respectively.[20] The mediation analysis adjusted for all variables in the primary model.

Analyses were conducted by the NRN Data Coordinating Center (RTI International) using R statistical software version 3.5.1 (Feather Spray, Vienna, Austria).

Results

Study population

During the study period, 2,277 infants were born between $22^{0/7}$ and $26^{6/7}$weeks' gestation and met initial inclusion criteria. Infants seen more than four months outside of the target neurodevelopmental assessment window of 22–26 months CA were excluded (n=77) and those without follow-up data were deemed lost to follow-up (n=300, 13.2%). The final analytic cohort included 1,900 infants; 583 died before follow-up assessment and 1,317 had complete neurodevelopmental assessments. Compared to infants in the analytic cohort, those lost to follow-up were slightly older, had higher birth weights, higher Apgar scores, and lower rates of severe brain injury (Supplemental table 1).

In the final cohort, 1,218 (64.1%) infants were exposed to ICC, 528 (27.8%) to DCC, and 154 (8.1%) to UCM (Figure 1). Baseline characteristics differed among the three groups (Table 1). For example, the proportion of infants exposed to antenatal steroids was lower in the ICC group and the proportion of infants who received PPV or intubation was lowest in the DCC group.

Primary and secondary outcomes

Compared to ICC, DCC-exposed infants had significantly lower adjusted odds of death or severe NDI (DCC: 36.3% versus ICC: 50.3%; aOR 0.64, 95% CI 0.50–0.83) (Table 2). A statistically significant difference was not observed in the primary outcome for the remaining two comparisons (UCM versus ICC and DCC versus UCM) (Table 2).

DCC-exposed infants had a significantly lower adjusted odds of death prior to follow-up compared to ICC-exposed infants (DCC: 22.4% versus ICC: 34.3%; aOR 0.61, 95% CI 0.46–0.81) (Table 3). There was no statistically significant difference in severe NDI between infants exposed to DCC versus ICC (16.7% versus 23.0%; aOR 0.74, 95% CI 0.52–1.05). There were no differences in secondary outcomes when comparing UCM to ICC or DCC. The results of the COVID-19-informed sensitivity analysis found no change in the primary outcome (Supplemental table 2).

Mediation analysis

Compared to ICC, DCC directly reduced death or severe NDI (average direct effect −0.063 after adjustment, p=0.012) with no indirect effect on the primary outcome via severe IVH (average indirect effect −0.009, p=0.52). No statistically significant direct or indirect effects were found in the remaining comparisons.

Discussion

In this large, contemporary observational study, exposure to DCC compared to ICC was associated with a significantly decreased odds of the composite outcome of death or severe NDI. The association was not mediated via severe IVH.

We have previously reported associations between umbilical cord management approaches and short-term outcomes. These studies highlighted practice variation across the NRN and demonstrated a benefit of DCC. [12] [13] In the current cohort, only 27.8% of infants were exposed to DCC, which may reflect provider preferences, literature interpretation, or desire for additional follow-up data. The impetus for the current study was sparse literature describing neurodevelopmental outcomes following different forms of cord management, particularly in the extremely preterm infant population. Comparing DCC and ICC, Mercer et al evaluated outcomes of 161 infants <32 weeks' gestation at 18–22 months' CA (77% of the original cohort) using the Bayley-III and found improved motor function following DCC.[6] Recently published data from APTS reported a reduced risk of death or disability at two years CA after DCC compared to ICC (RR 0.83 95% CI 0.72, 0.95) and a 39% reduction in the composite outcome of death or severe NDI.[9] Although our study is observational, the results similarly support DCC over ICC. The other two published trials report long-term outcomes comparing DCC and UCM among preterm infants. Rabe et al assessed children at two (n=39, 67% of the original cohort) and three and a half years (n=29, 50% of the original cohort) and found no differences in Bayley-III scores.[7] However, the inclusion of infants born from $27^{0/7}$ to $32^{6/7}$ weeks' gestation, a more mature population compared to our study, and small sample size may contribute to these findings. Katheria et al reported that among 135 toddlers assessed at 18 months (69% of the original cohort), infants randomized to UCM had higher language and cognitive scores than infants randomized to DCC.[8] Neurodevelopmental outcomes from Katheria's multicenter randomized controlled trial of UCM versus DCC are not yet known.[11] Aside from the APTS findings, published studies of neurodevelopmental outcomes are from trials limited by small samples sizes (29–263 infants) from single institutions, high attrition rates, variation in neurodevelopmental assessment measures, and a wide age range at the time of assessment, making comparisons challenging. The current study uses a large, multicenter cohort with higher rates (>86%) of in-person, standardized neurodevelopmental assessments to demonstrate the effectiveness of umbilical cord management approaches in premature infants outside the context of a trial.

Data regarding cord management techniques and IVH are evolving. The largest trial comparing DCC to ICC and associated meta-analysis reported comparable rates of severe IVH following either exposure.[21] [22] In contrast, the largest trial comparing DCC and UCM was stopped early due to increased severe IVH rates among UCM randomized infants. [11] We reported an association between UCM and severe IVH in the NRN.[12] While a recent meta-analysis comparing umbilical cord management strategies reported that DCC may be beneficial, particularly with regard to hematologic measures, it found no differences between UCM and ICC or DCC in survival or severe morbidities, including IVH.[23]

The increased severe IVH rates with UCM exposure, which have not been appreciated following DCC exposure, have informed guidelines supporting DCC.[24] We completed a pre-specified mediation analysis to further understand the relationship between cord management, severe IVH, and death or severe NDI, specifically to examine whether severe IVH mediates the exposure-outcome relationship. Relative to ICC, we found that exposure to DCC reduced death or severe NDI by 6.3 percentage points, which was not mediated by severe IVH. Within the other exposure comparisons (UCM versus ICC and DCC versus UCM), there was no difference in death or severe NDI and severe IVH was not a mediator.

This study has limitations. As a retrospective observational study, causality cannot be assigned and results are hypothesis generating. In the unadjusted comparisons, DCC-exposed infants had more favorable baseline characteristics, such as higher antenatal steroid exposure rates and lower receipt of resuscitative interventions. Despite model adjustments for variables prior to the exposure, residual confounding may influence study results. Those exposed to ICC may have been sicker at birth or experienced bradycardia after ICC, either of which may prompt more resuscitation. Comparisons with UCM should be interpreted cautiously given the small number of exposed infants. Additionally, this study lacks information surrounding the reason a specific cord management approach was chosen as these decisions are informed by individual clinical scenarios and local center policies. Studies examining long-term outcomes are at risk for attrition bias. In the current study this bias was compounded by the COVID-19 pandemic and associated impact on follow-up assessments, which was evident in the sensitivity analysis cohort that had a loss to follow-up rate of 9.9%, a lower rate compared to the primary cohort. Notably, the sensitivity analysis did not change the results.

Strengths of this study include detailed information on infants born at 15 academic centers across the United States. During the study period, 1,900 infants met inclusion criteria, making this the largest observational study to compare long-term neurodevelopmental outcomes following the three approaches to cord management. Previous studies of long-term outcomes have not included all possible pairwise comparisons of approaches to cord management to discern which approach is most beneficial for ELBW infants. Additionally, this study utilizes in-person, comprehensive, standardized neurodevelopmental assessments by trained examiners. These data further support the effectiveness of DCC in the real-world, clinical context.

In conclusion, in this large, contemporary, observational study of infants born <27 weeks' gestation, DCC was associated with improvement in the primary composite outcome of death or severe NDI at 22–26 months' CA compared to ICC. The protective effect of DCC on death or severe NDI was not mediated by severe IVH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data collected at participating sites of the NICHD Neonatal Research Network were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data included in this study. On behalf of the NRN, RTI International had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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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.

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Key Points

What is already known on this topic

Comparisons of short-term in-hospital outcomes following exposure to different forms of umbilical cord management in extremely preterm infants have shown delayed cord clamping to be beneficial compared to immediate cord clamping or umbilical cord milking. Published data about neurodevelopmental outcomes among extremely preterm infants following exposure to different forms of cord management are limited.

What this study adds

Compared to immediate cord clamping, delayed cord clamping may be beneficial for outcomes at 22 to 26 months' corrected age.

How this study might affect research, practice, or policy

This retrospective study, which captures clinical care and outcomes outside the context of a randomized clinical trial, provides further evidence supporting delayed cord clamping as a beneficial practice and hospital policy for extremely preterm infants.

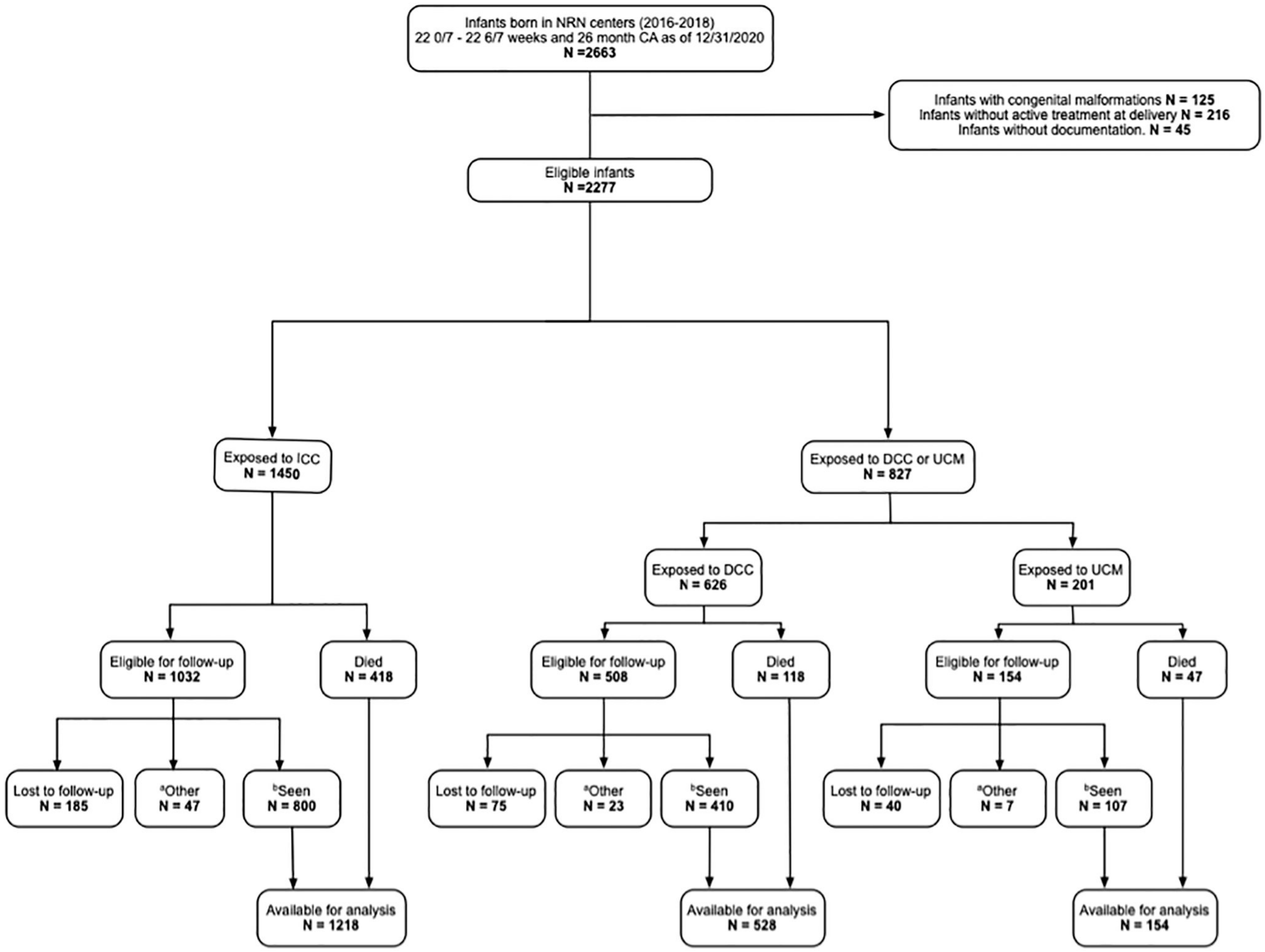

Figure 1.

Patient identification flowchart. *Infants seen but outside of the 18–30-month CA window. †Infants seen and examination window closed on or before 31/12/2020. DCC, delayed cord clamping; UCM, umbilical cord milking.

Table 1.

Sociodemographic and perinatal-neonatal characteristics

Characteristics	Exposure (%)			p value+		
	ICC (N=1218)	DCC (N=528)	UCM (N=154)	DCC vs. ICC	UCM vs. ICC	DCC vs. UCM
Neonatal characteristics						
Gestational age in weeks [mean weeks, (SD)]	24.9 (1.2)	25.1 (1.2)	25.0 (1.2)	0.005	0.97	0.10
Birth weight in grams [mean grams, (SD)]	702 (171)	732(173)	722 (159)	0.001	0.10	0.67
Small for gestational age	9.7%	6.8%	7.1%	0.05	0.38	0.86
Male sex	51.7%	51.0%	52.6%	0.79	0.86	0.78
Multiple births	26.0%	24.6%	30.5%	0.55	0.25	0.14
Age at follow up assessment [mean months, (SD)]	24.5 (2.1)	24.3 (2.2)	25.2 (2.1)	0.05	0.0004	< 0.0001
Sociodemographic characteristics						
Race/Ethnicity				0.55	< 0.0001	< 0.0001
Asian	2.6%	1.9%	7.1%			
Black, non-Hispanic	42.6%	44.3%	8.4%			
Hispanic	20.2%	10.8%	14.9%			
Other	2.0%	3.6%	4.6%			
White, non-Hispanic	32.2%	39.0%	64.3%			
Unknown/Not reported	0.5%	0.4%	0.7%			
Maternal Insurance				0.001	<0.0001	<0.0001
Private	36.5%	47.8%	59.7%			
Public	60.2%	50.7%	33.1%			
Other	3.4%	1.5%	7.1%			
Maternal education				0.04	0.96	0.23
Less than high school	15.2%	10.2%	6.5%			
High school degree	25.5%	23.3%	17.5%			
Partial college/trade/tech	24.5%	31.8%	28.6%			
College degree or higher	18.1%	22.7%	36.4%			
Missing	16.8%	11.9%	11.0%			
Multilingual at home	1.5%	2.9%	0%	< 0.0001	0.52	0.01
Missing due to death	34.4%	22.4%	30.7%			
Under state supervision	2.6%	3.4%	2.0%	< 0.0001	0.45	0.03
Missing due to death	34.4%	22.4%	30.7%			
Perinatal characteristics						
Limited or no prenatal care	14.5%	11.2%	7.8%	0.07	0.02	0.29
Diabetes prior to pregnancy	5.1%	2.7%	3.3%	0.02	0.43	0.78
Gestational diabetes	3.6%	2.9%	3.3%	0.47	1.00	0.79

Characteristics	Exposure (%)			p value+		
	ICC (N=1218)	DCC (N=528)	UCM (N=154)	DCC vs. ICC	UCM vs. ICC	DCC vs. UCM
Hypertension during pregnancy	26.9%	25.2%	21.4%	0.48	0.17	0.39
PIH	9.8%	12.7%	9.1%	0.08	0.89	0.26
Antenatal steroids	88.2%	96.6%	98.7%	< 0.0001	< 0.0001	0.28
Antenatal MgSO4	77.7%	88.8%	94.2%	< 0.0001	< 0.0001	0.07
Neonatal delivery characteristics						
1-minute Apgar score ≤4	75.5%	62.5%	67.3%	<0.0001	0.04	0.29
5-minute Apgar score ≤4	33.6%	23.3%	29.4%	<0.0001	0.32	0.14
Delivery room interventions						
PPV	91.8%	87.0%	97.3%	0.003	0.01	0.0001
Intubation	77.4%	70.4%	91.3%	0.003	< 0.0001	< 0.0001
Chest Compressions	5.7%	3.7%	4.7%	0.11	0.85	0.63
Epinephrine	2.8%	1.9%	3.4%	0.40	0.60	0.35
Among survivors beyond 12 hours after birth						
Severe brain injury	28.4%	24.0%	34.7%	0.08	0.12	0.01
Severe IVH[a]	22.9%	19.8%	29.9%	0.19	0.06	0.01
Cystic PVL	6.5%	5.3%	7.5%	0.37	0.60	0.31
Porencephalic cyst	2.1%	1.9%	0.7%	1.00	0.35	0.47
Ventriculomegaly	11.7%	10.3%	12.1%	0.45	0.89	0.55
Late onset sepsis	27.1%	24.7%	28.2%	0.30	0.77	0.39
Necrotizing enterocolitis	11.6%	12.2%	11.4%	0.74	1.00	0.89
Severe ROP[b]	17.3%	16.3%	14.0%	0.69	0.43	0.66
Among survivors at 36 weeks PMA						
Severe BPD[c]	11.6%	13.3%	11.9%	0.40	0.87	0.87

Abbreviations: BPD = bronchopulmonary dysplasia, ICC = Immediate cord clamping, DCC = Delayed cord clamping, UCM = Umbilical cord milking, PIH = Pregnancy induced hypertension, IVH = Intraventricular hemorrhage, PVL = Periventricular leukomalacia, PPV = Positive pressure ventilation, PMA = post menstrual age, ROP = retinopathy of prematurity.

[a]Severe IVH - grade III or IV

[b]Severe ROP- undergone ophthalmologic intervention for ROP or having retinal detachment

[c]Grade 3 BPD – requiring mechanical ventilation at 36 weeks corrected age

[+]p-values based on t-test/Wilcoxon rank sum test for continuous variables and Fisher’s exact test for categorical variables. Data presented as n (%) for categorical variables and median (SD) for continuous variables.

Table 2.

Associations between cord management practices and death or severe NDI

	Death or severe NDI (%)[a]		Adjusted OR (95% CI)
	DCC (N=528)	ICC (N=1218)	
DCC vs. ICC	36.3%	50.3%	0.64 (0.50, 0.83)
	UCM (N=154)	ICC (N=1218)	
UCM vs. ICC	46.3%	50.3%	0.83 (0.51, 1.36)
	DCC (N=528)	UCM (N=152)	
DCC vs. UCM	36.4%	46.3%	0.80 (0.43, 1.49)

Abbreviations: CI =confidence interval, DCC = Delayed cord clamping, ICC = Immediate cord clamping, NDI = Neurodevelopmental impairment, OR = Odds Ratio, UCM = Umbilical cord milking.

[a]The N indicates the total number of infants in the cohort exposed to the umbilical cord management practice listed. The fractional N reports the number of infants with death or severe NDI over the number of infants in the cohort in whom the primary outcome could be assessed.

Variables in the model include a priori variables associated with death or NDI (gestational age, race/ethnicity, maternal education, and antenatal steroids), those that differed in the bivariate comparison of DCC vs ICC and occurred before the exposure (insurance, limited or no prenatal care, diabetes prior to pregnancy, pregnancy induced hypertension and antenatal magnesium), sex, SGA, and birth year, with NRN center as a random effect.

Table 3.

Associations of cord management practices with secondary outcomes

Characteristics	Exposure N (%)			DCC/ICC aOR (95% CI)	UCM/ICC aOR (95% CI)	DCC/UCM aOR (95% CI)
	ICC (%)	DCC N (%)	UCM (%)			
Mortality[a]	418/1218 (34.3%)	118/528 (22.4%)	47 /154 (30.5%)	0.61 (0.46, 0.81)	0.66 (0.39, 1.11)	0.77 (0.42, 1.42)
Severe NDI[b]	175 / 761 (23.0%)	64 /383 (16.7%)	21 / 100 (21.0%)	0.74 (0.52, 1.05)	1.12 (0.62, 2.03)	0.72 (0.33, 1.55)
Moderate or severe CP[c]	97 / 796 (12.2%)	43 /406 (10.6%)	9 / 106 (8.5%)	0.85 (0.58, 1.25)[d]	0.67 (0.33, 1.37)[d]	1.28 (0.60, 2.71)
CP classification				1.01 (0.73, 1.40)	1.02 (0.59, 1.76)	0.91 (0.41, 2.02)
None	608 / 800 (76.0%)	317 / 406 (78.1%)	81 / 106 (76.4%)			
Mild	115 / 800 (14.4%)	52 / 406 (12.8%)	17 / 106 (16.0%)			
Moderate	45 / 800 (5.6%)	24 / 406 (5.9%)	6 / 106 (5.7%)			
Severe	32 / 800 (4.0%)	13 / 406 (3.2%)	2 / 106 (1.9%)			
Cognitive Bayley-3 score <70	156 / 778 (20.1%)	57 / 398 (14.3%)	20 / 104 (19.2%)	0.72 (0.50, 1.04)	1.23 (0.65, 2.31)	0.62 (0.28, 1.36)
Cognitive Bayley-3 score <85	391 / 778 (50.3%)	164 / 398 (41.2%)	44 / 104 (42.3%)	0.88 (0.68, 1.18)	1.08 (0.62, 1.91)	0.94 (0.50, 1.75)
Motor Bayley-3 score <70	165 / 764 (21.6%)	67 / 384 (17.5%)	19 / 102 (18.6%)	0.76 (0.53, 1.09)	0.85 (0.45, 1.62)	0.94 (0.41, 2.16)
Moderate to severe language delay (Language Bayley-3 <70)	257 / 770 (33.4%)	111 / 386 (28.8%)	28 / 103 (27.2%)	0.92 (0.67, 1.25)	1.03 (0.60, 1.77)	1.03 (0.50, 2.10)
Bilateral blindness	11 / 800 (1.4%)	5 / 408 (1.2%)	1 / 106 (.9%)	0.89 (0.31, 2.58)[d]	0.68 (0.09, 5.34)[d]	1.30 (0.15,11.27)[d]
Hearing impairment	24 / 778 (3.1%)	11 / 390 (2.8%)	2 / 103 (1.9%)	0.91 (0.44, 1.88)[d]	0.62 (0.14, 2.67)[d]	1.47 (0.32, 6.72)[d]

Abbreviations: aOR=adjusted odds ratio, Bayley-3 = Bayley Scales of Infant Development, CP = Cerebral palsy, DCC = Delayed cord clamping, ICC = Immediate cord clamping, NDI = Neurodevelopmental impairment, UCM = Umbilical cord milking.

[a] Mortality before assessment at 22–26 months' corrected age.

[b] Severe NDI-severe cerebral palsy (CP) [Gross Motor Function Classification System (GMFCS) >=4], cognitive BSID III <70, motor BSID scores <70, bilateral blindness despite corrective lens, or bilateral hearing impairment with or without amplification

[c] Moderate or severe CP-GMFCS >=2

[d] Model did not converge, was nearly unidentifiable, or variance-covariance matrix was not positive-definite, so raw Odds Ratios are report.

Variables in the model include a priori variables associated with death or NDI (gestational age, race/ethnicity, maternal education, and antenatal steroids), those that differed in the bivariate comparison of DCC vs ICC and occurred before the exposure (insurance, multilingual at home, limited or no prenatal care, diabetes prior to pregnancy, pregnancy induced hypertension and antenatal magnesium) and age at follow-up assessment and birth year, with NRN center as a random effect. Age at follow up assessment and multilingual at home were not included in the model assessing mortality