A Comparison of Strategies for Managing the Umbilical Cord at Birth in Preterm Infants

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Objective To evaluate the rates of practice, and the associations between different cord management strategies at birth (delayed cord clamping [DCC], umbilical cord milking [UCM], and early cord clamping [ECC]) and mortality or major morbidity, rates of blood transfusion, and peak serum bilirubin in a large national cohort of very preterm infants.

Study design We retrospectively studied preterm infants <33 weeks of gestation admitted to the Canadian Neonatal Network between January 2015 and December 2017. Patients who received ECC (<30 seconds), UCM, or DCC (≥30 seconds) were compared. Multiple generalized linear/quantile logistic regression models were used.

Results Of 12 749 admitted infants, 9729 were included; 4916 (50.5%) received ECC, 394 (4.1%) UCM, and 4419 (45.4%) DCC. After adjustment for potential confounders identified between groups in univariate analyses, the odds of mortality or major morbidity were higher in the ECC group when compared with UCM group (aOR, 1.18; 95% CI, 1.03-1.35). Mortality and intraventricular hemorrhage were associated with ECC as compared with DCC (aOR, 1.6 [95% CI, 1.22-2.1] and aOR, 1.29 [95% CI, 1.19-1.41], respectively). The odds of severe intraventricular hemorrhage were higher with UCM compared with DCC (aOR, 1.38; 95% CI, 1.05-1.81). Rates of blood transfusion were higher with ECC compared with UCM and DCC (aOR, 1.67 [95% CI, 1.31-2.14] and aOR, 1.68 [95% CI, 1.35-2.09], respectively), although peak serum bilirubin levels were not significantly different.

Conclusions Both DCC and UCM were associated with better short-term outcomes than ECC; however, the odds of severe intraventricular hemorrhage were higher with UCM compared with DCC. *(J Pediatr 2020;225:58-64)*.

The approach to umbilical cord management of preterm infants at birth has shifted from routine immediate clamping to delayed cord clamping (DCC) and umbilical cord milking (UCM) to enable placental transfusion to the infants at birth.[1] Early cord clamping (ECC) has been practiced for decades, but deprives the newborn infant of the multiple merits of placental transfusion. ECC does not stand on a physiologic basis, but rather a perceived need for early resuscitation and/or as a perceived part of the active management of labor.[2-5] Professional organizations such as the International Liaison Committee on Resuscitation, Neonatal Resuscitation Program, and American College of Obstetricians and Gynecologists have recommended DCC for 30-60 seconds for most preterm infants.[6-8] This recommendation has been reinforced by a recent meta-analysis showing decreased mortality and numbers of blood transfusions in preterm infants receiving DCC as opposed to ECC.[9] However, there are situations when DCC is contraindicated (eg, interrupted placental circulation) and others when the evidence for its use is still lacking (eg, nonvigorous infants requiring resuscitation). In such situations, ECC may still be practiced.[6-8]

An alternative strategy for placental transfusion, UCM, has not been adopted as widely as DCC despite clinical trials showing its benefits for the short-term outcomes of preterm infants.[10-12] Although UCM could fit well as an alternative method for placental transfusion, the lack of large-scale clinical trials and concerning data from animal studies showing nonphysiologic swings in the systemic arterial pressure and cerebral blood flow at birth have limited its use.[1,6,13] The few

BPD	Bronchopulmonary dysplasia
CNN	Canadian Neonatal Network
DCC	Delayed cord clamping
ECC	Early cord clamping
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
UCM	Umbilical cord milking

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small clinical trials that have compared UCM with DCC in preterm infants have shown that short-term outcomes for both techniques were similar, except for a higher incidence of intraventricular hemorrhage (IVH) in the DCC group.[14-17] The latter finding contradicts the most recent clinical trial, which was stopped because of a significant increase in severe IVH associated with UCM in extremely preterm infants.[18]

Our objective for this study was to examine the associations between different cord management strategies and mortality or major morbidity, rates of blood transfusions, and peak serum bilirubin levels in very preterm infants.

Methods

We carried out a retrospective cohort study of very preterm infants (<33 weeks of gestation) admitted to neonatal intensive care units (NICUs) participating in the Canadian Neonatal Network (CNN) database between January 2015 and December 2017. Preterm infants who received ECC (<30 seconds), UCM, or DCC (≥30 seconds) were identified. Infants with a palliative care plan, those with major congenital anomalies, and those missing cord clamping data were excluded.

We examined maternal, perinatal, and neonatal data including antenatal, delivery, resuscitation, postnatal course, and short-term outcomes for eligible infants who received ECC, UCM, or DCC at birth. Gestational age was defined as the best estimate based on obstetric history, obstetric examination, and first prenatal ultrasound examination. Maternal baseline characteristics included maternal diabetes and hypertension/preeclampsia. Perinatal baseline characteristics included maternal receipt of steroids and magnesium sulfate, singleton pregnancy, prolonged rupture of membranes, sex, gestational age at delivery, and outborn vs inborn status. Short-term clinical outcomes included birth weight, Apgar score, intubation, surfactant use, admission temperature, inotrope use within 48 hours, Scores for Neonatal Acute Physiology, peak serum bilirubin level, blood transfusion, ventilation, IVH, bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity, patent ductus arteriosus, late-onset sepsis, necrotizing enterocolitis (NEC), and mortality. Grades of IVH were defined as per Papile et al.[19] Severe IVH was defined as IVH grade ≥3. BPD was defined as any respiratory support at 36 weeks' corrected age or at the time of transfer to another medical facility if that occurred before 36 weeks' corrected age.[20] Severe retinopathy of prematurity was defined as stage ≥3 according to the International Classification or requiring treatment.[21] NEC was defined according to Bell criteria, and those with stage ≥2 were included in this study.[22] Mortality was defined as any death before discharge from the NICU; and major morbidity included BPD, severe IVH, NEC, severe retinopathy of prematurity, or late-onset sepsis.

Data on individual infants were collected as part of the ongoing CNN data collection system including 30 participating NICUs. At all affiliated sites, demographics and outcome data were collected from patient charts by trained research assistants using a computerized data entry program according to standardized outcome definitions.[23] In the digital standardized form, the time period from birth until cord clamping (in seconds) was recorded for infants. ECC was defined as clamping the cord at <30 seconds and DCC was defined as clamping the cord at ≥30 seconds. Cord milking was defined as milking of the cord 3-5 times from placenta toward the baby at a rate of 5-10 cm/second and reported as "yes" or "no" without a specifying how many times or how long the umbilical cord segment was milked. Data were collected on each infant until death or discharge from the NICU and transmitted electronically to the CNN coordinating center, where they were stored. The CNN database has been reported to have very high reproducibility and internal consistency.[24]

For the CNN database, data collection was approved by each institution's research ethics board or institutional quality improvement committee, as appropriate. The retrospective secondary analysis using data from the database for this study was approved by the Research Ethics Board at the IWK Health Centre in Halifax and the CNN Executive Committee.

Statistical Analyses

Descriptive statistics were used to describe the study population. Maternal and infant characteristics were compared among the 3 cord management strategy groups using the χ^2 test for categorical variables and the F-test or Kruskal-Wallis test, as appropriate, for continuous variables. Pairwise comparisons of the characteristics between the strategy groups were further conducted using the χ^2 test for categorical variables and the Student *t* test or Wilcoxon rank-sum test, as appropriate, for continuous variables. Trends in the usage rates of the 3 cord management strategies over study years were examined using the Cochran-Armitage trend test. We examined group differences in the outcomes in univariate analysis using the χ^2 test for categorical outcomes and the Student *t* test or Wilcoxon rank-sum test, as appropriate, for continuous ones. To further determine associations between the outcomes and the cord management strategy groups, we applied multiple logistic regression models for binary outcomes and linear regression or quantile regression models for normally distributed or heavily skewed continuous outcomes, respectively. The generalized estimating equation was used for the multiple regression analyses to account for the clustering of patients within each site. Potential confounders, identified in the univariate analysis and adjusted for in the regression models, included gestational age, small for gestational age, cesarean delivery, prolonged rupture of membranes >24 hours, antenatal magnesium sulphate use, antenatal steroid use, and maternal hypertension. Data management and statistical analyses were performed using SAS 9.4 (SAS institute Inc, Cary, North Carolina). A 2-sided *P* value of <.05 was used to specify statistical significance without adjustment for multiple comparisons.

Results

Of 12 749 patients admitted to the CNN during the 3-year study period, 9729 infants were included in the study. A total of 4916 (50.5%) received ECC, 394 (4.1%) received UCM, and 4419 (45.4%) received DCC (**Figure 1**). Significant increases occurred in the rates of DCC and UCM practiced over the study years ($P < .001$), with almost one-half of patients receiving DCC in 2017 (**Figure 2**; available at www.jpeds.com).

On univariate analyses, significant differences were seen between the 3 study groups in gestational age, small for gestational age, use of antenatal steroids and magnesium sulfate, maternal hypertension, prolonged rupture of membranes, and cesarean deliveries (**Table I**). The clinical outcomes during hospital stay for infants in each of the 3 groups are shown in **Table II**. After adjustment for potential confounders identified by univariate analyses, mortality was higher in the ECC group compared with the DCC group (aOR, 1.60; 95% CI, 1.22-2.10), and mortality or major morbidity was higher in the ECC group compared with the UCM group (aOR, 1.18; 95% CI, 1.03-1.35) (**Table III**).

Further comparison of the outcomes between groups after adjustment for confounding variables revealed the following.

ECC vs UCM

Infants who received ECC had higher odds of Apgar scores of <4 at 5 minutes (aOR, 1.53; 95% CI, 1.04-2.24) and intubation at birth (aOR, 1.62; 95% CI, 1.27-2.07); had lower admission temperatures (adjusted difference in mean −0.07°C; 95% CI, −0.11 to −0.02); and had higher odds of receiving blood transfusions (aOR, 1.67; 95% CI, 1.31-2.14) (**Table III**).

ECC vs DCC

Infants who received ECC had significantly lower birth weight (adjusted difference in mean of −16 grams; 95% CI, −24, to −8 grams); and higher odds of Apgar scores <4 at 5 minutes (aOR, 2.30; 95% CI, 1.73-3.06), Scores for Neonatal Acute Physiology scores >20 (aOR, 1.80; 95% CI, 1.42-2.28), surfactant use (aOR, 1.40; 95% CI, 1.26-1.57), inotropic support in the first 48 hours (aOR, 2.07; 95% CI, 1.58-2.70), blood transfusion (aOR, 1.68; 95% CI, 1.35-2.09), IVH (aOR, 1.29; 95% CI, 1.19-1.41), severe IVH (aOR, 1.33; 95% CI, 1.13-1.56), late-onset sepsis (aOR, 1.33; 95% CI, 1.20-1.48), patent ductus arteriosus (aOR, 1.14; 95% CI, 1.01-1.27), and mortality (aOR, 1.6; 95% CI, 1.22-2.10) (**Table III**).

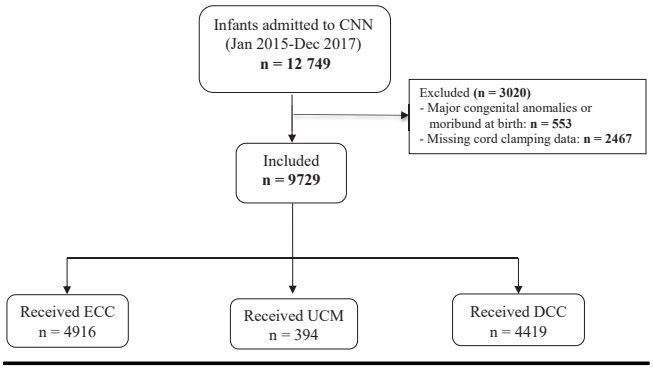

Figure 1. Study flow chart.

UCM vs DCC

Infants receiving UCM had higher odds of intubation at birth (aOR, 1.43; 95% CI, 1.07-1.91), surfactant use (aOR, 1.26; 95% CI, 1.04-1.53), Scores for Neonatal Acute Physiology scores on admission >20 (aOR, 1.49; 95% CI, 1.10-2.02), and severe IVH (aOR, 1.38; 95% CI, 1.05-1.81) than those who received DCC. However, infants who received UCM had higher admission temperature than those who received DCC (adjusted difference in mean 0.05°C; 95% CI, 0.01-0.09°C).

There were no associated increases in peak bilirubin levels in the DCC or UCM when compared with the ECC group. In addition, neither of the placental transfusion practices was associated with increased morbidity compared with ECC (**Table III**).

A subgroup analysis was performed for the extremely preterm infants (<28 weeks of gestation). Of these, 1633 infants received ECC, 152 received UCM, and 1052 received DCC. Comparison of the 3 cord management strategy groups revealed similar results to those reported for the overall cohort (**Table IV**; available at www.jpeds.com).

Discussion

In this large national cohort study, we identified higher odds of the composite outcome of mortality or major morbidity associated with ECC when compared with UCM. We also found higher odds of mortality, IVH, and sepsis for ECC compared with DCC. Higher numbers of blood transfusions were associated with those who received ECC as compared with UCM and DCC. The benefits of UCM and DCC were not associated with significant increases in peak serum bilirubin. Severe IVH was associated with ECC and UCM as compared with DCC. The practices of DCC and UCM increased over the study period.

In a previous study from the CNN, Lodha et al reported a decreased risk for the composite outcome of severe neurological injury or mortality in extremely low gestational age neonates who received DCC compared with those who received ECC.[25] However, that study was restricted to preterm infants <28 weeks of gestation, and its population was mostly born before the full implementation of DCC as the standard of care following the latest International Liaison Committee on Resuscitation and Neonatal Resuscitation Program guidelines.[6,7] In our study, despite increased rates of placental transfusion practices in Canadian NICUs over the 3-year

Table I. Comparison of baseline characteristics

Characteristics	ECC (n = 4916)	UCM (n = 394)	DCC (n = 4419)	*P* value (ECC vs UCM)	*P* value (ECC vs DCC)	*P* value (UCM vs DCC)
Maternal diabetes	14.8	14.9	15.6	.97	.31	.72
Maternal hypertension	18.8	21.9	20.8	.14	**.01**	.62
Preeclampsia	12.7	16.5	13.7	**.03**	.18	.12
Singleton	69.9	71.8	71.1	.42	.19	.77
Antenatal steroids	87.6	94.9	93.4	**<.01**	**<.01**	.25
Magnesium sulfate	45.6	58.4	46.7	**<.01**	.3	**<.01**
PROM >24 hours	22.9	23.4	25.3	.82	**<.01**	.40
Cesarean delivery	67.9	67.5	55.5	.88	**<.01**	**<.01**
Gestational age in weeks	29 (27-31)	29 (26-31)	30 (28-31)	**.01**	**<.01**	**<.01**
Gestational age <28 weeks	33.2	38.6	23.8	.03	**<.01**	**<.01**
Male	54.9	52.4	55.1	.34	.81	.30
Small for gestational age	11.0	13.0	9.9	.23	.07	.05
Outborn	12.8	2.8	5.0	**<.01**	**<.01**	.05

PROM, prolonged rupture of membranes.
Values are percent or median (IQR).

study period, 44% of infants still received ECC in 2017. Despite the proven benefits of DCC, the compliance with DCC still represents an area for improvement but is consistent with reported literature.[26-28] The uncertainty about the value of DCC for infants with perinatal depression, who do not breathe at birth, may have led to a high degree of noncompliance and a preference for ECC. This finding was clearly demonstrated in the largest randomized controlled study conducted to date, where nonadherence to DCC reached 26%.[26] A survey from the US reported DCC was practiced in 73% of preterm vaginal births.[27] In the Netherlands, DCC was reported in 54% of preterm deliveries and only 19% in cesarean deliveries.[28] Other factors that may have contributed to the high use of ECC include contraindications for DCC and resistance to, or slow adoption of, change.

In our study, the rate of the composite outcome of mortality or major morbidity was higher in the ECC compared with the UCM group. Previous systematic reviews of randomized controlled trials have suggested that UCM could decrease the risk of all grades IVH, BPD, and NEC, among other benefits, in comparison with ECC.[10-12] We found significantly higher mortality in the ECC group vs the DCC group, supporting the results of the latest systematic review, which included 2834 infants from 18 trials.[9] We also found that DCC was associated with better stabilization of preterm infants after birth; and reduction of morbidities such as all grades IVH, severe IVH, late-onset sepsis, patent ductus arteriosus, and the

Table II. Clinical outcomes during hospital stay for preterm infants <33 weeks of gestation

Outcomes	ECC (n = 4916)	UCM (n = 394)	DCC (n = 4419)	ECC vs UCM*	ECC vs DCC*	UCM vs DCC*
Birth weight, grams	1267 (464)	1207 ± 445	1371 ± 440	.01	<.01	<.01
Apgar score at 1 min	5 (2-7)	6 (3-8)	7 (5-8)	<.01	<.01	<.01
Apgar score <4 at 5 min	8.7 (423/4863)	4.3 (17/394)	3.2 (139/4404)	<.01	<.01	.21
Intubation at birth	30.4 (1490/4894)	23.6 (93/394)	14.1 (621/4413)	<.01	<.01	<.01
Chest compression	3.05 (150/4916)	2.54 (10/394)	2.1 (93/4419)	.57	<.01	.57
Epinephrine	2.47 (121/4894)	0.25 (1/394)	0.23 (10/4413)	<.01	<.01	.91
Surfactant use	47.8 (2350/4916)	46.4 (183/394)	34 (1503/4419)	.6	<.01	<.01
Admission temperature, °C	36.6 ± 0.78	36.7 ± 0.61	36.7 ± 0.70	<.01	<.01	.79
Inotropic support in first 48 hours	8.6 (423/4916)	6.1 (24/394)	3.4 (151/4419)	.08	<.01	<.01
SNAP II score >20	18 (874/4858)	16.2 (64/394)	10.5 (463/4395)	.38	<.01	<.01
Peak bilirubin level, mmol/dL	156.4 ± 46.0	154.5 ± 42.8	161.8 ± 45.4	.41	<.01	<.01
Blood transfusion	36.6 (1798/4916)	31.5 (124/394)	21.7 (957/4419)	.04	<.01	<.01
No. of transfusions (for those who received)	3 (1-6)	3 (2-6)	2 (1-4)	.78	<.01	.005
Necrotizing enterocolitis	4.0 (197/4914)	4.3 (17/394)	3.3 (144/4418)	.77	.054	.26
Mechanical ventilation	53.8 (2647/4916)	47 (185/394)	37.4 (1652/4419)	<.01	<.01	<.01
BPD	28.9 (1306/4522)	26.2 (96/367)	25 (1058/4241)	.27	<.01	.61
IVH	31.7 (1309/4131)	33.5 (111/331)	25 (867/3478)	.49	<.01	<.01
Severe IVH	8.5 (350/4131)	8.8 (29/331)	5.4 (188/3478)	.85	<.01	.01
Late-onset sepsis	12.5 (616/4916)	12.4 (49/394)	7.5 (330/4419)	.96	<.01	<.01
Severe ROP	10.9 (252/2306)	11 (22/200)	7.3 (129/1773)	.96	<.01	.06
PDA	31.97 (1560/4879)	29.01 (114/393)	22.25 (980/4404)	.22	<.01	<.01
Mortality	7.93 (390/4916)	7.36 (29/394)	3.48 (154/4419)	.68	<.01	<.01
Mortality or major morbidity	40.6 (1998/4916)	37.3 (147/394)	32.6 (1439/4419)	.19	<.01	.06

PDA, patent ductus arteriosus; *ROP*, retinopathy of prematurity; *SNAP*, Scores for Neonatal Acute Physiology.
Values are mean ± SD, median (IQR), or percent (N/n).
**P* value.

Table III. Clinical outcomes during hospital stay for preterm infants <33 weeks of gestation after adjustment

Outcomes	ECC vs UCM	ECC vs DCC	UCM vs DCC
Apgar score <4 at 5 min	**1.53 (1.04 to 2.24)**	**2.30 (1.73 to 3.06)**	1.51 (0.93 to 2.45)
Intubation at birth	**1.62 (1.27 to 2.07)**	**2.32 (1.8 to 2.98)**	**1.43 (1.07 to 1.91)**
Surfactant use	1.11 (0.96 to 1.29)	**1.40 (1.26 to 1.57)**	**1.26 (1.04 to 1.53)**
Inotropic support in first 48 hours	1.25 (0.76 to 2.06)	**2.07 (1.58 to 2.70)**	1.65 (0.88 to 3.09)
SNAP II score >20	1.20 (0.90 to 1.60)	**1.80 (1.42 to 2.28)**	**1.49 (1.10 to 2.02)**
Blood transfusion	**1.67 (1.31 to 2.14)**	**1.68 (1.35 to 2.09)**	1.01 (0.71 to 1.42)
Necrotizing enterocolitis	0.94 (0.69 to 1.29)	0.94 (0.70 to 1.27)	1.00 (0.69 to 1.44)
Mechanical ventilation	**1.31 (1.08 to 1.60)**	**1.53 (1.26 to 1.85)**	1.16 (0.94 to 1.44)
Bronchopulmonary dysplasia	1.09 (0.88 to 1.35)	1.04 (0.89 to 1.21)	0.95 (0.76 to 1.19)
IVH	1.14 (0.91 to 1.41)	**1.29 (1.19 to 1.41)**	1.14 (0.94 to 1.37)
Severe IVH	0.96 (0.74 to 1.26)	**1.33 (1.13 to 1.56)**	**1.38 (1.05 to 1.81)**
Late-onset sepsis	1.07 (0.79 to 1.43)	**1.33 (1.20 to 1.48)**	1.25 (0.92 to 1.69)
Severe ROP	1.04 (0.76 to 1.43)	1.31 (1.00 to 1.72)	1.26 (0.87 to 1.81)
Patent ductus arteriosus	1.42 (1.04 to 1.96)	**1.14 (1.01 to 1.27)**	0.80 (0.60 to 1.07)
Mortality	1.20 (0.72 to 2.01)	**1.60 (1.22 to 2.1)**	1.33 (0.80 to 2.21)
Mortality or major morbidity	**1.18 (1.03 to 1.35)**	1.15 (0.97 to 1.37)	0.98 (0.83 to 1.16)
Adjusted difference in mean/median (95% CI)			
Birth weight, grams	−13 (−37 to 11)	**−16 (−24 to −8)**	−3 (−27 to 22)
Admission temperature, °C	**−0.07 (−0.11 to −0.02)**	−0.02 (−0.06 to 0.01)	**0.05 (0.01 to 0.09)**
Peak bilirubin level, mmol/dL	1.4 (−4.0 to 6.8)	0.2 (−1.7 to 2.0)	−1.2 (−5.8 to 3.4)
No. of blood transfusions*	0.62 (−0.08 to 1.32)	**0.62 (0.40 to 0.84)**	0 (−0.75 to 0.75)

Values are aOR and 95% CI and were obtained based on the multiple logistic regression model with a generalized estimating equation approach to account for the clustering of patients within each site.
Variables adjusted for gestational age, small for gestational age, cesarean delivery, prolonged rupture of membrane >24 hours, magnesium sulfate ($MgSO_4$), antenatal steroid use, and maternal hypertension.
Difference in mean/median were estimated based on linear/quantile regression with a generalized estimating equation approach.
*Difference in median.

need for blood transfusions. These findings were still demonstrated in the subgroup analysis of the extremely preterm infants <28 weeks of gestation. Some of these findings, such as higher Apgar scores, less need for blood transfusion, and lower NEC and IVH rates, have been reported previously.[9,12,29] In our study, DCC was not associated with a significant increase in peak serum bilirubin levels or decrease in admission temperature when compared with ECC. In addition, no single morbidity was more frequent in the DCC group. Our data support the results of the largest randomized controlled trial to date that found less mortality and less blood transfusion without an increase in the rates of phototherapy in the DCC group compared with the ECC.[26]

An important result of our study was that UCM, compared with DCC, was significantly associated with higher rates of severe IVH. This finding was also noticed in the subgroup of preterm infants <28 weeks of gestation without a corresponding increase in the acuity score on admission. Katheria et al, in a randomized controlled trial comparing UCM with DCC, reported a higher incidence of severe IVH (22%) in a subgroup of 93 preterm infants <28 weeks of gestation who received UCM as compared with only 4% in 89 infants who received DCC ($P < .0007$). Their study was stopped because of this concern.[18] The authors attributed the increased severe IVH in the extremely preterm infants to their lack of cerebral autoregulation and the possible inflammatory role of the possible associated chorioamnionitis. In newborn lambs, Blank et al noted UCM caused large fluctuations in mean carotid artery pressure and blood flow without an effect on pulmonary blood flow.[13] Previous studies that did not find a difference in IVH rates between infants receiving UCM and DCC were underpowered and included small numbers of preterm infants <28 weeks of gestation.[14-16] Studies that examined DCC and UCM as a combined intervention vs either ECC or DCC alone did not show an increase in the rates of IVH.[30-32]

Placental transfusion practices seem to be associated with better outcomes when compared with ECC, with DCC remaining the practice of choice whenever feasible. This outcome was shown before to be related to improved physiological transition of the cardio-pulmonary systems at birth, not just to the added blood volume.[2-5] Although our data did not show an increase in IVH associated with UCM in comparison with ECC, the association of severe IVH with UCM when compared with DCC is worrisome. The question of whether UCM would be preferable to ECC, especially in situations where DCC is contraindicated, remains unanswered and needs further research.

The strengths of our study include its large population of very preterm infants (9729 infants), a national cohort with good generalizability, and comparison of the 3 prevailing strategies for managing the cord at birth in preterm infants. Limitations include the study's retrospective nature, which did not allow us to investigate the indications for receiving each intervention. Despite our efforts to adjust for potential confounders, infants who received ECC or UCM could have been sicker at birth than those who received DCC. There were missing data regarding cord clamping in the database and we could not address the different durations of DCC. Because the reasons for practicing ECC, DCC, or UCM in individual

infants were not collected, residual confounding may thus be a factor. We have not done any adjustment for multiple comparisons. Finally, because of the small size of the UCM group, there was the potential for type I error.

In conclusion, placental transfusion practices for preterm infants <33 weeks of gestation, whether by DCC or UCM, increased over years in Canadian NICUs. Nevertheless, 44% of infants still received ECC in 2017. Both DCC and UCM were associated with better short-term outcomes than ECC; however, the odds of severe IVH were significantly higher with UCM vs DCC. We suggest that, when DCC is feasible, UCM is a less desirable intervention than DCC for very preterm infants. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Tuberous Sclerosis: From Phenotype to Genotype

Hurwitz S, Irwin B. White Spots in Tuberous Sclerosis. J Pediatr 1970;77:587-94.

Much was already understood in 1970 about tuberous sclerosis, including many of its classical phenotypic characteristics with skin, central nervous system, eye, heart, kidney, lung, and bone findings. Neurocutaneous stigmata of adenoma sebaceum, shagreen patches, periungual and gingival fibromas, and hypopigmented macules were described at the time. Hurwitz and Braverman detailed the cutaneous findings in 23 patients with tuberous sclerosis and compared pigmentary lesions in these children with those found in 55 children with neurologic disorders exclusive of tuberous sclerosis, and 100 neurologically typical children. The majority of children with tuberous sclerosis in their sample (78%) had hypopigmented macules, a finding in only one of the children in the comparator groups. There was considerable variability in the size and shape of the lesions in this sample compared with the classic lance-ovate shape similar to the leaf of the mountain ash tree described by Fitzpatrick et al in 1968, with additional description of confetti lesions, which are now recognized in the diagnostic criteria.[1,2]

Fifty years ago, there was appropriate emphasis on the clinical diagnosis of tuberous sclerosis and other neurocutaneous disorders. Clinical diagnosis of tuberous sclerosis using major and minor criteria remains an important tool, particularly when attempting to make rapid treatment decisions in a patient presenting with new-onset infantile spasms with neurocutaneous features. The increasing accuracy and availability of genetic testing has changed diagnostic practices for tuberous sclerosis. Importantly, the 2012 update in the diagnostic criteria for tuberous sclerosis complex includes genetic criteria, with identification of either a *TSC1* or *TSC2* pathogenic mutation sufficient to make a definitive diagnosis of tuberous sclerosis.[2] As genetic testing continues to evolve, the yield of these analyses continues to increase. Sanger sequencing enabled the detection of point mutations in coding regions and intron and exon boundaries of *TSC1* and *TSC2*, with a diagnostic yield of 75%-90% when combined with deletion and duplication analysis.[3] Next-generation sequencing *TSC1* and *TSC2* panels have even further increased the ability to identify pathogenic variants.[3] As genetic testing continues to expand in both availability and affordability, there will likely be further emphasis on early genetic diagnosis and genetic confirmation of clinical diagnosis. However, there is no substitute for evaluation and recognition of clinical features to guide further diagnostics.

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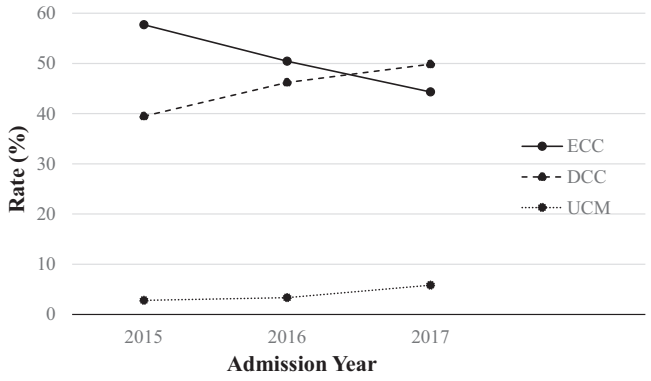

Figure 2. Trends in the rates of umbilical cord management strategies during study years.

Table IV. Clinical outcomes during hospital stay for preterm infants <28 weeks of gestation

Outcomes	ECC vs UCM	ECC vs DCC	UCM vs DCC
Apgar score <4 at 5 min	**2.11 (1.33 to 3.33)**	**2.04 (1.50 to 2.76)**	0.97 (0.55 to 1.71)
Intubation at birth	**1.67 (1.20 to 2.32)**	**2.00 (1.62 to 2.48)**	1.20 (0.80 to 1.79)
Surfactant use	1.41 (0.98 to 2.03)	**1.42 (1.18 to 1.72)**	1.01 (0.67 to 1.53)
Inotropic support in first 48 hours	0.94 (0.64 to 1.38)	**1.83 (1.39 to 2.40)**	**1.95 (1.17 to 3.26)**
SNAP II score>20	1.06 (0.70 to 1.60)	**1.43 (1.13 to 1.80)**	1.35 (0.81 to 2.24)
Blood transfusion	**1.97 (1.41 to 2.76)**	**1.56 (1.15 to 2.11)**	0.79 (0.49 to 1.29)
Necrotizing enterocolitis	0.97 (0.64 to 1.47)	1.09 (0.76 to 1.56)	1.12 (0.70 to 1.81)
Mechanical ventilation	1.09 (0.79 to 1.50)	1.37 (0.99 to 1.90)	1.26 (0.81 to 1.96)
Bronchopulmonary dysplasia	1.08 (0.70 to 1.65)	1.03 (0.87 to 1.23)	0.96 (0.61 to 1.50)
IVH	1.16 (0.76 to 1.79)	**1.20 (1.06 to 1.35)**	1.03 (0.68 to 1.55)
Severe IVH	0.83 (0.57 to 1.21)	**1.28 (1.01 to 1.61)**	**1.55 (1.07 to 2.23)**
Late-onset sepsis	1.08 (0.76 to 1.54)	**1.34 (1.16 to 1.55)**	1.24 (0.85 to 1.81)
Severe ROP	1.10 (0.75 to 1.61)	1.33 (0.98 to 1.79)	1.21 (0.79 to 1.86)
Patent ductus arteriosus	1.37 (0.86 to 2.17)	1.12 (0.98 to 1.27)	0.82 (0.55 to 1.22)
Mortality	1.06 (0.64 to 1.74)	**1.39 (1.07 to 1.82)**	1.32 (0.81 to 2.14)
Mortality or major morbidity	**1.80 (1.16 to 2.80)**	1.10 (0.87 to 1.39)	0.61 (0.37 to 1.01)
Adjusted difference in mean/median (95% CI)			
Birth weight, grams	−4 (−23 to 15)	**−18 (−28 to −8)**	−15 (−32 to 2)
Admission temperature, °C	−0.03 (−0.16 to 0.09)	**−0.10 (−0.15 to −0.04)**	−0.06 (−0.17 to 0.05)
Peak bilirubin level, mmol/dL	3.3 (−1.2 to 7.8)	1.5 (−1.7 to 4.7)	−1.8 (−6.0 to 2.5)
No. of blood transfusions*	1 (0.34 to 1.66)	1 (0.66 to 1.34)	0 (– 0.71 to 0.71)

ROP, retinopathy of prematurity; *SNAP*, Scores for Neonatal Acute Physiology.
Values are aOR (95% CI) and were obtained based on the multiple logistic regression model with generalized estimating equation approach to account for the clustering of patients within each site. Variables adjusted for gestational age, small for gestational age, cesarean delivery, prolonged rupture of membrane >24 hours, magnesium sulfate ($MgSO_4$), antenatal steroid, and maternal hypertension (associated with the exposure group in the univariate analysis).
Difference in mean/median were estimated based on linear/quantile regression with a generalized estimating equation approach.
*Difference in median.

Appendix

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