OBSTETRICS

Umbilical cord management in extremely preterm infants born by cesarean delivery

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BACKGROUND: Deferred cord clamping reduces mortality in preterm infants. However, there is a controversy about whether deferred cord clamping is as effective in cesarean delivery as in vaginal delivery.

OBJECTIVE: This study aimed to compare the mortality and short-term outcomes of extremely preterm singleton infants who received deferred cord clamping after cesarean delivery with those who received deferred cord clamping after vaginal delivery and those who received early cord clamping after cesarean delivery.

STUDY DESIGN: A national retrospective review of maternal, perinatal, and neonatal data of preterm infants born at <29 weeks of gestation who were admitted to units participating in the Canadian Neonatal Network between January 2015 and December 2022 was conducted. The rates and trends of deferred cord clamping (≥ 30 seconds) were evaluated, and the outcomes of infants who received deferred cord clamping after cesarean delivery were compared with (a) those who received deferred cord clamping after vaginal delivery and (b) those who received early cord clamping (<30 seconds) after caesarean delivery. The primary outcome was hospital mortality/severe brain injury (defined as grade 3/4 intraventricular hemorrhage and/or periventricular leukomalacia). Multivariate regression models with generalized estimating equations were used to account for clustering of infants within each site after adjusting for potential confounders.

RESULTS: Of 6137 infants included in the study, 1952 (31.8%) received deferred cord clamping after cesarean delivery, 1804 (29.4%) received deferred cord clamping after vaginal delivery, and 2381 (38.8%) received early cord clamping after cesarean delivery at a median gestational age of 27 (interquartile range, 25—28), 26 (interquartile range, 25—28) and 26 (interquartile range, 25—28) weeks, respectively. There was a slow increase in the practice of deferred cord clamping in cesarean delivery from 32% in 2015 to approximately 50% in 2021—2022. After adjustment for potential confounders, infants who received deferred cord clamping after cesarean delivery had lower odds of a composite of mortality/severe brain injury (281/1952 [14%]) than those who received deferred cord clamping after vaginal delivery (347/1804 [19%]; adjusted odds ratio, 0.69 [95% confidence interval, 0.54—0.87]) and those who received early cord clamping after cesarean delivery (543/2381 [23%]; adjusted odds ratio, 0.69 [95% confidence interval, 0.57—0.83]). Deferred cord clamping after cesarean delivery was not associated with changes in other adverse short-term outcomes.

CONCLUSION: Deferred cord clamping was associated with a reduction in a composite of mortality/severe brain injury in singleton preterm infants born at <29 weeks of gestation via cesarean delivery.

Key words: brain injury, cesarean delivery, deferred cord clamping, early cord clamping, morbidity, preterm infants, vaginal delivery

Introduction

Deferred cord clamping (DCC) for at least 30 to 60 seconds is recommended as the standard of care for most preterm infants, regardless of the mode of delivery.[1−3] DCC is known to reduce mortality and the need for blood transfusion.[4,5] However, there is a reluctance among many obstetrical providers to perform DCC in cesarean delivery (CD).[6] One of the reasons for the reluctance is the controversy in the literature of whether DCC is as effective in providing adequate placental transfusion in CD as it is in vaginal delivery (VD). The assumption of reduced effectiveness of DCC in CD could be related to the lack of uterine contractions, effect of maternal anesthesia/medications, and maternal hemodynamic status.[7,8] In a meta-analysis of 15 studies that included 8477 infants, CD was found to be significantly associated with higher placental residual blood volume (less transfusion to the infant) and less hemoglobin and hematocrit concentrations in the cord blood and newborns' peripheral blood than VD.[9] Aladangady et al[10] measured the blood volume in preterm infants born at <32 weeks of gestation who were randomized to DCC or early cord clamping (ECC) after VD and CD. Compared with infants who received ECC, the increased blood volume achieved by DCC was significantly higher in those born via VD, whereas the increased blood volume was modest and not statistically significant in those born by CD. The authors raised the concern of a possible reversal of blood flow between the placenta and infant because of uterine atonicity in CD.[10] The same finding was reported earlier in full-term infants who received DCC for >40 seconds after CD.[11] Kleinberg et al[12] reported no significant placental transfusion when the umbilical cord was delayed for ≥30 seconds after CD.

In contrast, other studies reported greater hemoglobin/hematocrit values in full-term infants who received DCC after an elective CD than in those who received ECC.[13,14]

0002-9378

https://doi.org/10.1016/j.ajog.2025.09.036

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AJOG at a Glance

Why was this study conducted?

There is a controversy about whether deferred cord clamping (DCC) in cesarean delivery improves the outcomes of extremely preterm infants, like in vaginal delivery. This study aimed to compare the mortality and major morbidities of extremely preterm singleton infants who received DCC after cesarean delivery with those who received DCC after vaginal delivery and those who received early cord clamping after cesarean delivery.

Key findings

The rate of DCC in cesarean delivery is increasing but is still suboptimal at approximately 50%. DCC in cesarean delivery was associated with a reduction in a composite of mortality/severe brain injury in extremely preterm infants without increasing the odds of infant adverse outcomes.

What does this add to what is known?

Our results support the practice of DCC for ≥30 seconds for extremely preterm infants born via cesarean delivery.

Apart from the Australian Placental Transfusion Study, most trials addressing DCC in preterm infants were hampered by the small sample size, especially in the extremely preterm infants.[4,15] In addition, these studies did not stratify the included infants by the mode of delivery and/or did not perform subgroup analysis to assess the effect of the mode of delivery. Moreover, there is a paucity of large studies addressing the degree of uptake and adherence to the recent guidelines and the outcomes of the recent change of practice in extremely preterm infants born via CD.

This study aimed to assess the rate and trend of practicing DCC in extremely preterm singleton infants born at <29 weeks of gestation via CD (DCC-CD) and compare their rates of mortality and short-term morbidities with those who received DCC after VD (DCC-VD) and those who received ECC after CD (ECC-CD). We hypothesized that infants in the DCC-CD group would have comparable outcomes with the DCC-VD group and better outcomes than the ECC-CD group.

Materials and methods

Study population

This national retrospective cohort study included singleton preterm infants born at <29 weeks of gestation and admitted to neonatal intensive care units (NICUs) participating in the Canadian Neonatal Network (CNN) database between January 1, 2015, and December 31, 2022. Infants who received DCC (≥30 seconds) after CD were compared with those who received DCC after VD and those who received ECC (<30 seconds) after CD. Infants with major congenital anomalies, those who were moribund at birth, those who were planned for palliative care, those who were outborn, those who received cord milking, those who received ECC after VD, or those who had missing cord management data were excluded.

Study variables and outcomes

The variables that were analyzed were maternal and infant baseline characteristics and short-term neonatal outcomes before hospital discharge.

The primary outcome was a composite of mortality before discharge/severe brain injury defined as grade 3/4 intraventricular hemorrhage according to the Papile classification[16] and/or periventricular leukomalacia. The secondary outcomes included rates and trends of DCC-CD; admission temperature; peak serum bilirubin level; number of blood transfusions; bronchopulmonary dysplasia defined as supplemental oxygen treatment at 36 weeks of corrected age or at the time of transfer to another medical facility if that occurred before 36 weeks of corrected age[17]; late-onset sepsis defined as any positive blood and/or cerebral spinal fluid culture for bacteria, viruses, or fungi after 2 days of age; necrotizing enterocolitis (stage II or greater) defined according to the Bell criteria[18]; treated or severe retinopathy of prematurity (stage ≥3) defined according to the international classification[19]; treated patent ductus arteriosus defined as patients receiving medical or surgical treatment; severe brain injury; and mortality before discharge. Gestational age was defined as the best estimate based on the first prenatal ultrasound examination, obstetrical history, and obstetrical examination.

Data sources

Study data were obtained from the CNN database, which included 30 affiliated Canadian NICUs during the study period. The perinatal demographics and outcome data were collected by trained research assistants from patient records using a computerized data entry program and standardized definitions.[20] Data of each infant from admission to the NICU to discharge or death were transmitted electronically to the CNN coordinating center. The CNN database was shown to have very high internal consistency and reproducibility.[21]

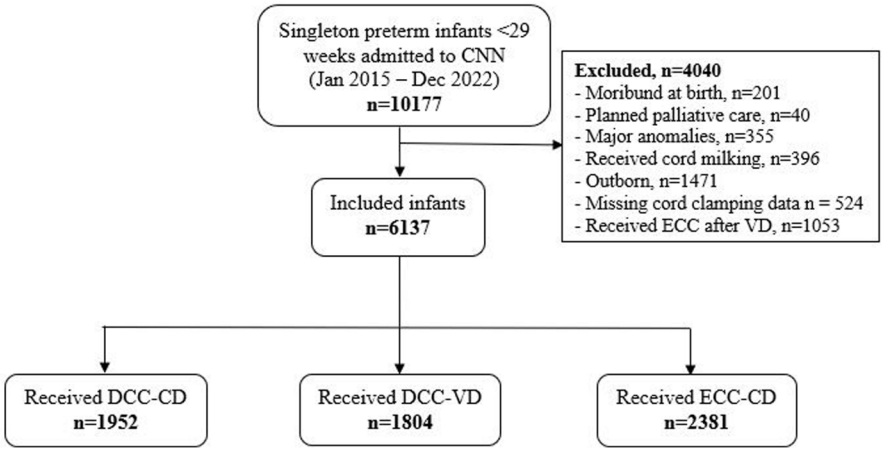
Ethics

Required approval for CNN data collection was granted by each research ethics board or institutional quality improvement committee. Secondary analysis of the database for this study was approved by the research ethics board of the Izaak Walton Killam Health Centre (project number: 1029520) and the executive committee of the CNN.

Statistical analysis

Descriptive statistics were used to compare the clinical characteristics and outcomes of the DCC-CD group to the other 2 study groups. The chi-square test was used for categorical variables, and the Student *t* test or Wilcoxon rank-sum test was used for continuous variables. To assess the differences in

FIGURE 1
Patient flowchart



CD, cesarean delivery; *CNN*, Canadian Neonatal Network; *DCC*, deferred cord clamping; *DCC-CD*, deferred cord clamping after cesarean delivery; *DCC-VD*, deferred cord clamping after vaginal delivery; *ECC*, early cord clamping; *ECC-CD*, early cord clamping after cesarean delivery; *VD*, vaginal delivery.

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the trends in practice, Cochran-Armitage trend tests were used for DCC-CD (all CD as the denominator) and DCC-VD (all VD as the denominator) from 2015 to 2022. Outcome comparisons between each 2 groups stratified by CD/DCC were performed using multiple logistic regression models for a binary outcome, linear regression models for a normally distributed continuous outcome, and generalized linear models with a log link for a nonnormally distributed continuous outcome, adjusted for potential confounders. Prespecified variables for adjustment included maternal hypertension, antenatal steroid use, gestational age, small for gestational age, prolonged rupture of membranes, and labor initiation. Only variables occurring before the intervention (ie, DCC or ECC) were included for adjustment. Generalized estimating equations were used to account for the clustering of patients within each site. A 2-sided *P* value of <.05 indicated statistical significance for the primary outcome. To assess the significance of differences in the secondary outcomes, a modified Bonferroni (Holm-Bonferroni) method was used to account for multiple comparisons. Data management and statistical analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC).

TABLE 1
Maternal and infant baseline characteristics

Variable	DCC-CD (n=1952)	DCC-VD (n=1804)	*P* value	DCC-CD (n=1952)	ECC-CD (n=2381)	*P* value
Maternal age (y), mean (SD)	31.9 (5.6)	30.8 (5.5)	<.01	31.9 (5.6)	31.9 (5.6)	.96
Maternal diabetes mellitus, n (%)	264 (14%)	233 (13%)	.30	264 (14%)	303 (13%)	.57
Maternal hypertension, n (%)	657 (34%)	105 (6%)	<.01	657 (34%)	668 (28%)	<.01
Antenatal steroids, n (%)	1892 (97%)	1723 (96%)	.02	1892 (97%)	2233 (94%)	<.01
PROM > 24 hours, n (%)	520 (28%)	752 (42%)	<.01	520 (28%)	725 (32%)	<.01
Chorioamnionitis, n (%)	521 (28%)	736 (43%)	<.01	521 (28%)	557 (25%)	.06
Gestational age, median (IQR)	27 (25–28)	26 (25–28)	<.01	27 (25–28)	26 (25–27)	<.01
Male, n (%)	1051 (54%)	981 (54%)	.73	1051 (54%)	1298 (55%)	.64
SGA, n (%)	335 (17%)	23 (1%)	<.01	335 (17%)	416 (17%)	.78
Labor initiation			<.01			.62
No labor	1005 (51%)	13 (1%)		1005 (51%)	1231 (52%)	
Spontaneous labor	890 (46%)	1666 (92%)		890 (46%)	1097 (46%)	
Augmented labor	10 (1%)	81 (4%)		10 (1%)	7 (0%)	
Induced labor	37 (2%)	43 (2%)		37 (2%)	39 (2%)	
Labor, n (%)	937 (48%)	1790 (99%)	<.01	937 (48%)	1143 (48%)	.95

CD, cesarean delivery; *DCC*, deferred cord clamping; *DCC-CD*, deferred cord clamping after cesarean delivery; *DCC-VD*, deferred cord clamping after vaginal delivery; *ECC*, early cord clamping; *ECC-CD*, early cord clamping after cesarean delivery; *PROM*, prolonged rupture of membranes; *SGA*, small for gestational age; *VD*, vaginal delivery.

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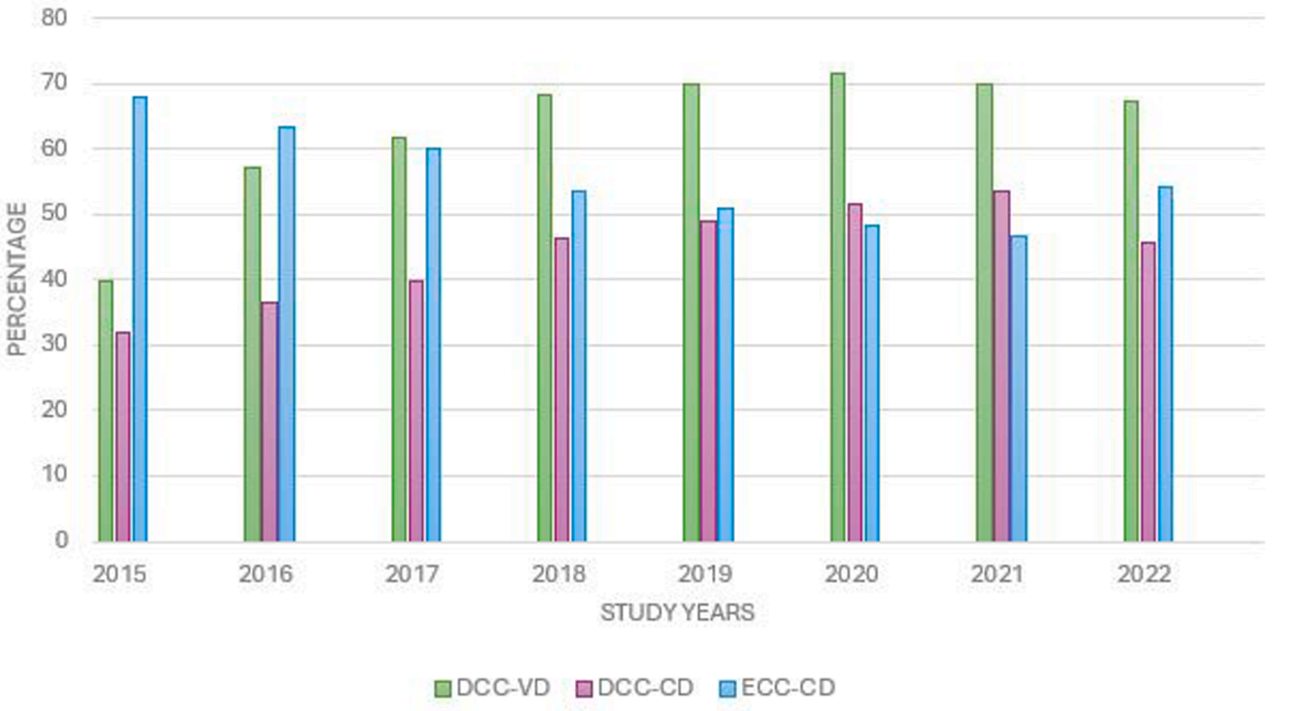
Results

A total of 10,177 singleton infants born at <29 weeks of gestation were admitted to participating NICUs during the study period. After exclusion, 6137 infants were included in the study. Of these infants, 1952 received DCC-CD (31.8%), 1804 (29.4%) received DCC-VD and 2381 (38.8%) received ECC-CD (Figure 1). The median gestational ages were 27 weeks (interquartile range [IQR], 25—28) in the DCC-CD group and 26 weeks (IQR, 25—28) in the DCC-VD group ($P<.01$). Median gestational ages were 27 weeks (IQR, 25—28) in the DCC-CD group and 26 weeks (IQR, 25—27) in the ECC-CD group ($P<.01$). Maternal and infant baseline characteristics of the different study groups are presented in Table 1. There was a slow increasing trend in the rates of DCC in both VD and CD over the study period. The rate of practicing DCC in CD increased from 32% in 2015 to approximately 50% in 2021 and 2022 ($P<.0001$ for the trend over the study period). The rate of DCC in VD increased from 40% of all VDs in 2015 to approximately 69% in 2021 and 2022 ($P<.0001$) (Figure 2).

Infants who received DCC-CD had lower odds of the composite outcome of mortality/severe brain injury (281/1952 [14%]) than those who received DCC-VD (347/1804 [19%]; unadjusted odds ratio [OR], 0.71 [95% confidence interval (CI), 0.57—0.88]). After adjustment, the adjusted OR was still significant (0.69 [95% CI, 0.54—0.87]). The secondary outcomes of Apgar scores of <4 at 5 minutes, intubation at birth, surfactant use, score for acute neonatal physiology (SNAP) of >20, inotropic support in the first 48 hours, and length of hospital stay were significantly higher in the DCC-CD group after adjustment (Table 2). The odds of severe brain injury, late-onset sepsis, and peak serum bilirubin level were significantly lower in the DCC-CD group before and after adjustment, whereas the odds of the other secondary outcomes were not significantly different between the 2 groups (Table 2).

DCC-CD was associated with significantly lower odds of a composite of mortality/severe brain injury (281/1952 [14%]) than ECC-CD (543/2381 [23%]; unadjusted OR, 0.57 [95% CI, 0.48—0.67]). The difference remained significant after adjustment (adjusted OR, 0.69 [95% CI, 0.57—0.83]). The secondary outcomes of mortality, severe brain injury, Apgar scores of <4 at 5 minutes, intubation at birth, surfactant use, SNAP score of >20, inotropic

FIGURE 2
Rates of DCC-VD, DCC-CD, and ECC-CD by study years



Abbreviations: DCC-VD: infants who received deferred cord clamping after vaginal delivery | DCC-CD: infants who received deferred cord clamping after cesarean delivery | CD-ECC: infants who received early cord clamping after cesarean delivery

CD, cesarean delivery; *DCC*, deferred cord clamping; *DCC-CD*, deferred cord clamping after cesarean delivery; *DCC-VD*, deferred cord clamping after vaginal delivery; *ECC*, early cord clamping; *ECC-CD*, early cord clamping after cesarean delivery; *VD*, vaginal delivery.

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TABLE 2
Short-term outcomes with adjusted ORs comparing infants who received DCC after CD and those who received DCC after VD

Outcomes	DCC-CD (n=1952) n (%)	DCC-VD (n=1804) n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	*P* value[a]
Mortality/severe brain injury	281 (14.0%)	347 (19.0%)	0.71 (0.57–0.88)	0.69 (0.54–0.87)	.003[b]
Mortality	179 (9.0%)	174 (10.0%)	0.95 (0.69–1.30)	0.87 (0.60–1.26)	.41
Severe brain injury	141 (7.0%)	232 (13.0%)	0.53 (0.44–0.65)	0.60 (0.45–0.79)	.0006[b]
Apgar score of <4 at 5 min	140 (7.0%)	125 (7.0%)	1.04 (0.77–1.40)	1.57 (1.23–2.01)	.0008[b]
Intubation at birth	670 (34.0%)	590 (33.0%)	1.08 (0.92–1.26)	1.41 (1.18–1.67)	<.0001[b]
Surfactant use	1392 (71.0%)	1020 (57.0%)	1.91 (1.65–2.22)	1.66 (1.39–1.98)	<.0001[b]
SNAP II score of >20	465 (30.0%)	393 (28.0%)	1.12 (0.97–1.30)	1.52 (1.22–1.89)	<.0001[b]
Inotropic support (first 48 h)	176 (9.0%)	111 (6.2%)	1.51 (1.24–1.84)	1.73 (1.38–2.17)	<.0001[b]
Blood transfusion (yes/no)	1118 (57.0%)	966 (54.0%)	1.16 (1.04–1.30)	1.03 (0.89–1.20)	.37
NEC stage 2 or above	111 (6.0%)	115 (6.0%)	0.89 (0.73–1.08)	0.99 (0.84–1.17)	.80
BPD	974 (54.0%)	784 (48.0%)	1.30 (1.11–1.53)	1.11 (0.90–1.37)	.29
Late-onset sepsis	317 (16.0%)	366 (20.0%)	0.76 (0.66–0.88)	0.75 (0.62–0.91)	.007
Severe ROP	166 (12.0%)	174 (13.0%)	0.86 (0.70–1.06)	0.96 (0.70–1.31)	.69
PDA	989 (51.0%)	888 (49.0%)	1.07 (0.93–1.23)	1.12 (0.95–1.31)	.08
			Unadjusted MD (95% CI)	Adjusted MD (95% CI)[a]	*P* value
Admission temperature, median (IQR)	36.7 (36.4–37.0)	36.8 (36.5–37.1)	−0.11 (−0.18 to −0.05)	−0.03 (−0.11 to 0.04)	.38
			Unadjusted MR (95% CI)	Adjusted MR (95% CI)[a]	*P* value
Peak bilirubin level (mmol/L), median (IQR)	130.0 (110.0–155.5)	137.0 (115.0–163.0)	0.96 (0.93–0.98)	0.96 (0.93–0.99)	.03
Number of transfusions, median (IQR)	3 (2–5)	3 (2–5)	1.03 (0.94–1.12)	1.04 (0.95–1.15)	.36
Length of hospital stay, median (IQR)	71 (44–101)	68 (42–100)	1.04 (0.99–1.08)	1.05 (1.01–1.10)	.02

BPD, bronchopulmonary dysplasia; *DCC*, deferred cord clamping; *DCC-CD*, deferred cord clamping after cesarean delivery; *DCC-VD*, deferred cord clamping after vaginal delivery *IQR*, interquartile range; *MD*, mean difference; *MR*, mean ratio; *NEC*, necrotizing enterocolitis; *OR*, odds ratio; *PDA*, patent ductus arteriosus; *ROP*, retinopathy of prematurity; *SNAP*, score for acute neonatal physiology; *VD*, vaginal delivery.

[a] Adjusted for gestational age, small for gestational age, maternal hypertension, antenatal steroid use, prolonged rupture of membranes (>24 hours), labor initiation, and chorioamnionitis. Generalized estimating equation was used to account for within-site correction; [b] Still significant after modified Bonferroni correction (when adjusted for 18 comparisons). The *P* value is derived from the models that produced the adjusted OR.

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support in the first 48 hours, and blood transfusion were significantly lower in the DCC-CD group before and after adjustment (Table 3). Admission temperature and peak bilirubin levels were not significantly different between the DCC-CD group and ECC-CD group (Table 3).

Comment

Principal findings

This nationwide retrospective study investigated the trend and benefits of DCC-CD. The trend of practicing DCC-CD in extremely preterm infants born at <29 weeks of gestation has been increasing over time but is still suboptimal at approximately 50% of all CDs. DCC-CD was associated with reduced composite outcome of mortality/severe brain injury and other secondary outcomes compared with DCC-VD and ECC-CD without increased odds of hypothermia, hyperbilirubinemia, or major adverse effects.

Results and clinical implications

There has been a steady improvement in the overall trend of DCC-CD over the study period, from 32% in 2015 to approximately 50% in 2021–2022. Although this represents a positive sign, the practice of DCC-CD still falls far behind DCC-VD, which improved from 40% in 2015 to approximately 69% in 2021-2022. A survey from the Netherlands showed that obstetrical providers were reluctant to perform DCC-CD, with 81% preferring ECC compared with 3% to 25%

TABLE 3
Short-term outcomes with adjusted ORs comparing infants who received DCC after CD and those who received ECC after CD

Outcomes	DCC-CD (n=1952) n (%)	ECC-CD (n=2381) n (%)	Unadjusted OR	Adjusted OR (95% CI)[a]	*P* value[a]
Mortality/severe brain injury	281 (14%)	543 (23%)	0.57 (0.48–0.67)	0.69 (0.57–0.83)	.0005[b]
Mortality	179 (9%)	364 (15%)	0.56 (0.46–0.68)	0.70 (0.56–0.88)	.003[b]
Severe brain injury	141 (7%)	271 (12%)	0.59 (0.49–0.72)	0.68 (0.57–0.82)	.002[b]
Apgar score of <4 at 5 min	140 (7%)	305 (13%)	0.49 (0.36–0.66)	0.54 (0.39–0.76)	.0008[b]
Intubation at birth	670 (34%)	1235 (52%)	0.49 (0.38–0.62)	0.54 (0.41–0.71)	<.0001[b]
Surfactant use	1392 (71%)	1868 (78%)	0.68 (0.57–0.82)	0.77 (0.60–0.97)	.004[b]
SNAP II score of >20	465 (30%)	809 (40%)	0.60 (0.50–0.72)	0.68 (0.55–0.84)	.005
Inotropic support (first 48 h)	176 (9%)	395 (17%)	0.50 (0.38–0.65)	0.59 (0.44–0.78)	.003[b]
Blood transfusion (yes/no)	1118 (57%)	1765 (74%)	0.47 (0.39–0.56)	0.47 (0.37–0.59)	<.0001[b]
NEC stage 2 or above	111 (6%)	185 (8%)	0.72 (0.56–0.92)	0.77 (0.58–1.03)	.10
BPD	974 (54%)	1214 (60%)	0.81 (0.68–0.97)	0.90 (0.74–1.09)	.40
Late-onset sepsis	317 (16%)	498 (21%)	0.73 (0.61–0.89)	0.82 (0.65–1.03)	.07
Severe ROP	166 (12%)	283 (16%)	0.68 (0.51–0.91)	0.77 (0.55–1.07)	.23
PDA	989 (51%)	1297 (55%)	0.84 (0.72–0.98)	0.93 (0.78–1.11)	.70
			Unadjusted MD (95% CI)	Adjusted MD (95% CI)	*P* value
Admission temperature, median (IQR)	36.7 (36.4–37.0)	36.6 (36.2–36.9)	0.12 (0.03–0.21)	0.09 (0.00–0.19)	.048
			Unadjusted MR (95% CI)	Adjusted MR (95% CI)[a]	*P* value
Peak bilirubin level (mmol/L), median (IQR)	130.0 (110.0–155.5)	129.0 (109.0–155.0)	0.99 (0.96–1.03)	0.98 (0.94–1.01)	.19
Number of transfusions, median (IQR)	3 (2–5)	3 (2–6)	0.86 (0.75–0.98)	0.84 (0.74–0.95)	.02
Length of hospital stay, median (IQR)	71 (44–101)	78 (45–110)	0.95 (0.89–1.01)	0.97 (0.92–1.03)	.45

BPD, bronchopulmonary dysplasia; *DCC*, deferred cord clamping; *DCC-CD*, deferred cord clamping after cesarean delivery; *ECC*, early cord clamping; *ECC-CD*, early cord clamping after cesarean delivery; *IQR*, interquartile range; *MD*, mean difference; *MR*, mean ratio; *NEC*, necrotizing enterocolitis; *OR*, odds ratio; *PDA*, patent ductus arteriosus; *ROP*, retinopathy of prematurity; *SNAP*, score for acute neonatal physiology.

[a] Adjusted for gestational age, small for gestational age, maternal hypertension, antenatal steroid use, prolonged rupture of membranes (>24 hours), labor initiation, and chorioamnionitis. Generalized estimating equation was used to account for within-site correction; [b] Still significant after modified Bonferroni correction (when adjusted for 18 comparisons). The *P* value is derived from the models that produced the adjusted OR.

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preferring ECC after VD.[6] A recent quality improvement project conducted in the United States, which aimed to increase the rate of DCC in preterm infants born at <34 weeks of gestation, suggested that physicians' reluctancy to perform DCC-CD in preterm infants could be due to the lack of an experienced pediatric team at predelivery planning or infant status at birth. Other factors included, but were not limited to, lack of awareness of the benefits of DCC and gaps in knowledge in the DCC protocol.[22]

Here, our main objective was to explore the benefits associated with DCC-CD. The finding of an improved composite outcome of mortality/severe neurologic injury in the DCC-CD group compared with the DCC-VD group is at least reassuring. The assumption that the reduced mortality/severe brain injury could be attributed to an adventitious role of CD over VD for preterm infants is still debated in the literature. The mode of delivery was not shown to reduce mortality and was controversial in reducing severe brain injury in singleton preterm infants.[23–26]

We chose to primarily compare DCC-CD with DCC-VD to minimize the confounding by indication when DCC-CD is compared with ECC-CD, as it is perceived that sicker mothers and/or

compromised fetuses will receive urgent CD where ECC would be the preferred method of cord management. Therefore, the outcomes of these compromised infants are expected to be worse in the ECC-CD group. Moreover, the reduced severe brain injury and late-onset sepsis associated with DCC-CD in our study infants, despite the lower Apgar scores and the worse immediate postnatal outcomes than those who received DCC-VD, provide further reassurance to the practice of DCC in CD. Of note, the rate of blood transfusion was not significantly different between infants who received DCC-CD and those who received DCC-VD, providing indirect evidence for the effectiveness of placental transfusion in DCC-CD.

On the other hand, our study showed that DCC-CD was associated with a reduction in the composite of mortality/severe brain injury compared with ECC-CD. This is consistent with the latest individual patient data meta-analysis that showed a reduction in mortality after DCC compared with ECC that was not affected by the mode of delivery in the subgroup analysis.[5] The fact that blood transfusions were significantly lower in the DCC-CD group than in the ECC-CD group in our study further suggests the effectiveness of placental transfusion in CD.

It is noteworthy that DCC-CD was not associated with increased rates of hypothermia on admission compared with ECC-CD and DCC-VD. This finding is reassuring and addresses the concern raised by the latest meta-analysis that reported increased hypothermia after DCC in preterm infants born at <32 weeks of gestation.[5]

Research implications

As shown in our study, the rates of practicing DCC-CD are still suboptimal. To better guide clinical practice and support clinicians, there is a need for more research addressing placental transfusion in CD. This includes the optimal duration of DCC; utility of other methods of placental transfusion, such as physiological-based cord clamping; and extrauterine placental transfusion, particularly in very preterm infants.[27] These studies should equally explore related maternal outcomes (eg, postpartum hemorrhage, postpartum infection, and optimal timing of administration of uterotonic medication). Further research is needed to explore the best placental transfusion practice in emergent CD and when DCC is not feasible or contraindicated.

GLOSSARY

BPD, bronchopulmonary dysplasia
CD, cesarean delivery
CNN, Canadian Neonatal Network
DCC, deferred cord clamping
DCC-CD, deferred cord clamping after cesarean delivery
DCC-VD, deferred cord clamping after vaginal delivery
ECC, early cord clamping
ECC-CD, early cord clamping after cesarean delivery
IQR, interquartile range; MD, mean difference; MR, mean ratio
NEC, necrotizing enterocolitis
NICU, neonatal intensive care unit
OR, odds ratio
PDA, patent ductus arteriosus
PROM, prolonged rupture of membranes
ROP, retinopathy of prematurity
SGA, small for gestational age
SNAP, score for acute neonatal physiology
UCM, umbilical cord milking
VD, vaginal delivery

Strengths and limitations

The strengths of our study include being a large national study using a high-quality database. This study compared DCC-CD with DCC-VD to reduce confounding by indication if we mainly focused on comparing DCC-CD with ECC-CD. The added comparison of DCC-CD with ECC-CD further supports our findings.

Our study limitations include its retrospective design and the lack of documentation of indications of different cord management practices. Given our observational design, we cannot directly attribute outcomes to cord management practice but rather can explore associations. Physicians tend to immediately clamp and cut the cord if the infant is perceived to be compromised. Therefore, a risk of confounding by indication may exist when comparing DCC with ECC. The mode of delivery could, in theory, contribute to improved outcomes when DCC-CD was compared with DCC-VD. Despite our efforts to adjust for important confounders, there might be some that were unmeasured. Finally, we could not compare the maternal outcomes as they were not available in our database.

Conclusion

The results of this large national study demonstrate that DCC for extremely preterm singleton infants born at <29 weeks of gestation via CD was associated with a reduction in a composite of mortality/severe brain injury. DCC in CD was not associated with significant adverse neonatal outcomes compared with DCC in VD or ECC in CD.

CRediT authorship contribution statement

Walid I. El-Naggar: Writing — review & editing, Supervision, Methodology, Conceptualization. ■

Acknowledgments

We would like to thank the Canadian Neonatal Network (CNN) Coordinating Centre at the Maternal-Infant Care Research Centre, Mount Sinai Hospital, Toronto, Ontario, Canada, for providing organizational support to the CNN and this project. The CNN Coordinating Centre is supported by funding from the Canadian Institutes of Health Research and Mount Sinai Hospital.

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Received July 8, 2025; revised Sept. 9, 2025; accepted Sept. 19, 2025.

The names of the Canadian Neonatal Network and Canadian Preterm Birth Network Investigators are listed in the Acknowledgments.

This project was conducted with no specific financial support. The Canadian Institutes of Health Research (CIHR) funded the Canadian Preterm Birth Network (CPTBN; grant number: PBN 150642). Organizational support for the Canadian Neonatal Network (CNN) and the CPTBN was provided by the Maternal-Infant Care Research Centre at Mount Sinai Hospital in Toronto, Ontario, Canada. MiCare is supported by Mount Sinai Hospital, participating hospitals, and CIHR funding.

The funding bodies had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. We confirm the independence of the study researchers from the funders, and we confirm that all authors, external and internal, had full access to all data in the study and can take responsibility for the integrity of the data and the accuracy of the analysis.

The authors report no conflict of interest.

This study was presented at the Pediatric Academic Societies Meeting, Toronto, Ontario, Canada, May 2—6, 2024.

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