Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association of Early Caffeine Administration and Neonatal Outcomes in Very Preterm Neonates

Abhay Lodha, MD, MSc; Mary Seshia, MBChB; Douglas D. McMillan, MD; Keith Barrington, MD; Junmin Yang, MSc; Shoo K. Lee, MD, PhD; Prakesh S. Shah, MD, MSc; for the Canadian Neonatal Network

IMPORTANCE Advantages of caffeine for apnea of prematurity have prompted clinicians to use it prophylactically even before apnea.

OBJECTIVE To determine the effect of early initiation of caffeine therapy on neonatal outcomes in very preterm infants born in Canada.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted. Patients included preterm neonates born at less than 31 weeks' gestation admitted to 29 participating Canadian Neonatal Network neonatal intensive care units between January 1, 2010, and December 31, 2012.

EXPOSURES Neonates who received caffeine were divided into 2 groups based on the following timing of caffeine initiation: within the first 2 days after birth (early) and on or after the third day following birth (late).

MAIN OUTCOME AND MEASURE A composite of death or bronchopulmonary dysplasia.

RESULTS Of 5517 eligible neonates, 5101 (92.5%) received caffeine (early: 3806 [74.6%]; late: 1295 [25.4%]). There was no difference in weight or gestational age at birth between the groups. Neonates in the early group had decreased odds of a composite outcome of death or bronchopulmonary dysplasia (adjusted odds ratio [AOR], 0.81; 95% CI, 0.67-0.98) and patent ductus arteriosus (AOR, 0.74; 95% CI, 0.62-0.89). There was no difference between the groups in mortality (AOR, 0.98; 95% CI, 0.70-1.37), necrotizing enterocolitis (AOR, 0.88; 95% CI, 0.65-1.20), severe neurological injury (AOR, 0.80; 95% CI, 0.63-1.01), or severe retinopathy of prematurity (AOR, 0.78; 95% CI, 0.56-1.10).

CONCLUSIONS AND RELEVANCE In very preterm neonates, early (prophylactic) caffeine use was associated with a reduction in the rates of death or bronchopulmonary dysplasia and patent ductus arteriosus. No adverse impact on any other outcomes was observed.

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Author Affiliations: Department of Pediatrics and Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada (Lodha); Department of Pediatrics, University of Manitoba, Winnipeg, Manitoba, Canada (Seshia); Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada (McMillan); Department of Pediatrics, Université de Montréal, Montréal, Quebec, Canada (Barrington); Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada (Yang, Lee, Shah).

Group Information: The Canadian Neonatal Network group members are listed at the end of the article.

Corresponding Author: Abhay Lodha, MD, MSc, Department of Pediatrics, Foothills Medical Centre, University of Calgary, C211-1403 29 St NW, Calgary, AB T2N2T9, Canada (aklodha@ucalgary.ca).

Methylxanthines are the most commonly used medications for apnea of prematurity in neonates.[1-3] At least 84% of neonates who weigh less than 1000 g at birth and 25% of neonates who weigh less than 2500g at birth experience apnea during the newborn period.[4,5] Apneic episodes often occur on the first day after birth in infants associated with respiratory distress but are delayed and often commence between 3 to 7 days after birth in infants who initially present with respiratory distress syndrome. When used during the first 10 days after birth in preterm infants weighing less than 1250 g at birth for apnea of prematurity, caffeine reduced bronchopulmonary dysplasia (BPD) and increased the survival without neurodevelopmental disability at 18 to 24 months of age.[6,7] The possible mechanisms of action of caffeine on respiration include an increase in sensitivity to carbon dioxide, elevated metabolic rate, enhanced catecholamine activity, increased diaphragmatic contractility, decreased muscle fatigability, and diuresis via tubular adenosine A1 receptors.[8,9]

Since the publication of the Caffeine for Apnea of Prematurity[10] randomized clinical trial in 2006, clinical practice has changed in many centers and the use of caffeine for prophylactic purposes has increased (ie, administration is commenced very soon after birth or before a diagnosis of apnea of prematurity is made). Caffeine has short-term adverse effects that include increased heart rate, jitteriness, irritability,

and seizures.[8] Schmidt et al[10] reported that in premature infants, poor weight gain for the first 3 weeks after initiating caffeine therapy was a commonly encountered adverse effect. Caffeine had no effects on mortality before the first discharge.[10] Owing to the long half-life of caffeine and the prolonged exposure of preterm neonates, there may be some impact even after the drug is withdrawn. In previous studies, the use of caffeine for apnea of prematurity improved survival without neurodevelopmental impairments at the corrected ages of 18 to 21 months and 5 years of age.[7,11] Two studies have reported effects of the early use of caffeine and neonatal outcomes.[12,13] A single-center study of the early use of caffeine (<3 days) in preterm neonates reported decreased rates of BPD or death, reduced need for treatment of patent ductus arteriosus (PDA), and shorter duration of mechanical ventilation in the early caffeine group.[13] A secondary analysis of the Caffeine for Apnea of Prematurity Trial also showed that early initiation of caffeine at younger than 3 days was associated with short-term respiratory benefits but there was no difference in the effects on other outcomes.[14]

We hypothesized that the use of prophylactic caffeine (initiation within 2 days of birth) would provide similar benefits without evidence of short-term harm in neonates born at less than 31 weeks' gestational age. The goal of this study was to determine the association of early initiation of caffeine therapy in very preterm neonates and neonatal outcomes.

Methods

Design and Study Participants

This retrospective observational study cohort included all preterm neonates who were born at less than 31 weeks' gestational age and admitted to 29 participating neonatal intensive care units (NICUs) in the Canadian Neonatal Network (CNN) between January 1, 2010, and December 31, 2012. Neonates born outside a tertiary-level NICU, moribund neonates, those with major congenital anomalies, and neonates who died before day 3 after birth were excluded from the study. Data collection was approved by either the research ethics board or institutional quality improvement committee at each participating site. Parents/guardians did not provide consent owing to the retrospective nature of this study.

Data Collection

The data were collected as part of the CNN routine data collection.[15] Of a total of 30 tertiary NICUs in Canada, 29 participated in the CNN during the study period and all preterm neonates (<31 weeks) admitted to those NICUs were included in the study, subject to the inclusion criteria. Eligible preterm neonates who received caffeine were identified from the CNN database. The day of birth was defined as day of life 1. Based on the timing of caffeine initiation, patients were divided into the following 2 groups: early (neonates who received caffeine within the first 2 days after birth) and late (neonates who received caffeine starting ≥3 days after birth). Most of the neonates who are extubated from mechanical ventilators in the first 48 hours of life tend to receive early caffeine to avoid reintubation following apnea of prematurity. The usual practice in most of units is to administer a loading dose of 10 mg/kg of caffeine base, with a daily maintenance dose of 2.5 to 5 mg/kg initiated 24 hours after the loading dose. A small number of neonates may receive a second loading dose for recurrence of apnea and in an attempt to avoid intubation (data not collected). The data on daily use of caffeine was collected for each infant by data abstractors at each site as a yes/no variable. Neither the daily nor the total cumulative dose of caffeine received by the infant was collected. Other demographic and outcomes data were collected from the patient's medical record by trained research assistants at all affiliated sites using a computerized data entry program and standardized definitions according to the CNN manual.[16] Data were collected until death or discharge from the NICU. Data were transmitted electronically to the CNN coordinating center, where they were stored.

Outcomes

The primary outcome of this study was a composite of death or BPD. Secondary outcomes were death, BPD, severe retinopathy of prematurity (grade 3, > grade 3, or treated), severe neurological injury (defined as the presence of grade 3 or 4 intraventricular hemorrhage or parenchymal echolucency), periventricular echogenicity persisting beyond 21 days of age or periventricular leukomalacia, PDA, stage 2 or higher necrotizing enterocolitis (NEC), ventilation days, and oxygen days.

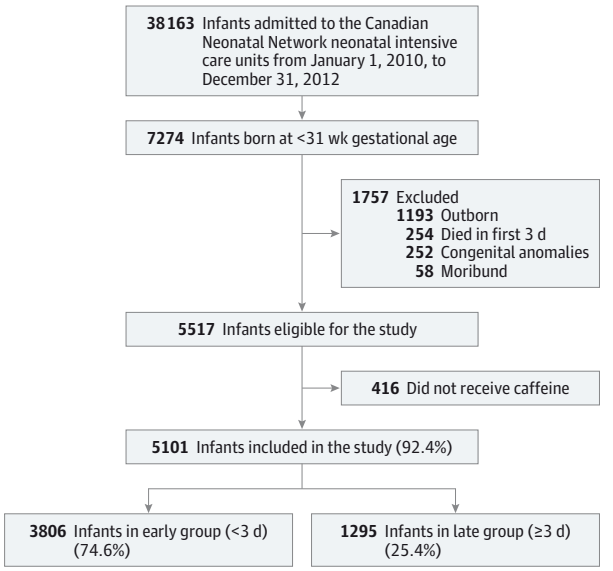
Definitions

Outcomes were defined according to the CNN data abstractor's manual. Gestational age was defined as the best estimate based on obstetric history, obstetric examination, and first prenatal ultrasonography examination.[17] Data on the severity of illness were collected using the Score for Neonatal Acute Physiology version II (SNAP-II).[18] Bronchopulmonary dysplasia was defined as supplemental oxygen use at 36 weeks' postmenstrual age or at discharge from the NICU.[17] Diagnosis of PDA was made clinically (a wide pulse pressure, prominent precordial pulsations, bounding pulses and continuous systolic murmur at the 2nd left parasternal area, and/or signs of heart failure), with or without echocardiography. Intraventricular hemorrhage was diagnosed and classified according to the Canadian Pediatric Society's Cranial Ultrasound Statement.[19] Retinopathy of prematurity was defined according to the international classification.[17] Necrotizing enterocolitis was defined according to Bell criteria[20] and was classified as medical or surgical. Small for gestational age was defined as birth weight smaller than the 10th percentile for the given gestational age. Duration of mechanical ventilation was defined as the total number of days during which the infant was receiving mechanical ventilation during any part of the day. Duration of noninvasive respiratory support was defined as the total number of days during which the infant received continuous positive airway pressure (CPAP), bilevel CPAP, or noninvasive ventilation. Total duration of oxygen use was defined as the total number of days during which the infant received supplemental oxygen. Length of stay was defined as the total number of days that an infant stayed in a NICU.

Statistical Analyses

Statistical analyses were performed with SAS version 9.2 software package (SAS Institute Inc). Maternal and infant demographic characteristics, perinatal risk factors, and the incidence of mortality and morbidities among neonates in the early and late groups were compared using Pearson χ^2 test for categorical variables and the *t* test for continuous variables. A Wilcoxon rank test (a nonparametric test) was used when continuous data were not normally distributed. Multivariable logistic regression analysis was used to examine the effect of significant outcomes from the univariate analysis of the early (<3 days) vs late (≥3 days) caffeine groups on the primary and secondary outcomes, with adjustment for various clinically significant predictors of neonatal morbidity and mortality including gestational age, small for gestational age, intubation on day 2 after birth, site, SNAP-II severity scores, and the use of surfactants. Some neonates only required CPAP and did not require intubation at birth. However, some of these neonates subsequently developed respiratory distress syndrome and required intubation on day 2 of life. Therefore, we included intubation on day 2 as an effect modifier in the model.

Figure. Flow Diagram of the Study Cohort



Results

Of the 38 163 neonates admitted to participating NICUs during the study, 7274 were born at less than 31 weeks' gestational age. Two hundred seventeen preterm infants received caffeine within 2 days of life and died before 3 days of age. A total of 5517 neonates (75.8%) were eligible for this study (**Figure**). A small group of neonates (n = 416) did not receive caffeine. Of the 5101 (92.5%) preterm neonates who received caffeine, 3806 (74.6%) were included in the early group and 1295 (25.4%) in the late group. The characteristics of the preterm neonates in the early and late groups are compared in **Table 1**. There were no differences in maternal characteristics between the early and late groups. There was also no significant difference in the basic characteristics between groups who did not receive caffeine (n = 416) vs groups who received caffeine (n = 5101). Apgar scores at 5 minutes were higher and SNAP-II scores were lower in neonates who received early caffeine. The median age of initiation of caffeine in the early and late groups was 1 day (interquartile range, 1-2 days) and 4 days (interquartile range, 3-8 days), respectively ($P < .01$). The total duration of exposure to caffeine was longer in the early group compared with the late group. More neonates in the late group received postnatal steroids.

The results of multivariable analyses for neonatal outcomes are reported in **Table 2**. The odds of the composite outcome of BPD or death were lower in the early caffeine group vs the late caffeine group. Most of this effect stemmed from the reduction of BPD because there was no difference in mortality between the 2 groups. Preterm neonates in the late group had a higher incidence of PDA and higher rates of surgical treatment for PDA compared with the early group. There was no difference in any of the other outcomes (severe neurological injury, NEC, severe retinopathy of prematurity, or mortality) between the 2 groups. Resource data from the 2 groups are compared in **Table 3**. Neonates in the late group stayed longer in the NICU and were more likely to have received mechanical ventilation, high-frequency ventilation, and oxygen for a longer period of time. The number of infants discharged home who received caffeine was similar in the 2 groups (Table 3). However, many of them were transferred to level 2 NICUs rather than home.

Discussion

Despite the lack of evidence from randomized clinical trials evaluating very early use of caffeine in preterm neonates, most of very preterm neonates in Canadian NICUs included in this study received caffeine within the first 2 days after birth. In this large population-based cohort, we identified no serious adverse effects with early (prophylactic) initiation of caffeine in preterm neonates (born at <31 weeks' gestational age) compared with those who received caffeine later. Preterm neonates in the early group had less incidence of PDA and required less surgical intervention. After adjustment for recorded clinical factors, the early caffeine administration was associated with reduction in the composite outcome of death or BPD, especially BPD. In individual outcomes, there were no differences in death, severe neurological injury, severe retinopathy of prematurity, and stage 2 or 3 NEC between the early-caffeine and late-caffeine groups.

It has become routine in many Canadian NICUs for preterm neonates born at less than 31 weeks' gestational age to be administered early-caffeine therapy to prevent apnea of prematurity and facilitate extubation. The practice of early extubation has increased during the last few years and it has been shown that early caffeine reduces reintubation.[21] Infants who

Table 1. Characteristics of Preterm Infants Included in the Study[a]

Variable	Caffeine Group, No. (%)		P Value
	Early (n = 3806)	Late (n = 1295)	
Antenatal steroids	3533 (94.4)	1173 (92.9)	.05
Multiples	1228 (32.3)	366 (28.3)	.01
Cesarean section	2321 (61.3)	778 (60.7)	.72
Gestational age, median (IQR), wk	28 (26-29)	28 (26-30)	.07
≤24	54 (1.4)	32 (3.2)	<.01
25-28	2273 (59.7)	717 (55.4)	
29-30	1479 (38.9)	535 (41.3)	
Birth weight, median (IQR), g	1070 (850-1310)	1050 (790-1360)	.66
Small for gestational age (<10th percentile)	340 (9.0)	139 (10.8)	.06
Female	1749 (46.1)	565 (43.8)	.15
Apgar score at 5 min, median (IQR)	8 (6-9)	7 (6-8)	<.01
SNAP-II score, median (IQR)	9 (5-16)	12 (5-22)	<.01
Intubation at birth	1363 (38.3)	427 (34.8)	.03
Surfactant	1557 (43.8)	536 (43.7)	.98
Duration of caffeine, median (IQR), d	37 (21-55)	30 (14-51)	<.01
Postnatal steroids	590 (15.5)	368 (28.4)	<.01
Air leak syndrome	124 (3.3)	74 (5.9)	<.01
Conventional ventilation on d 2	1496 (39.3)	496 (38.3)	.52
High-frequency ventilation on d 2	236 (6.2)	251 (19.4)	<.01
CPAP on d 2	1447 (38.0)	350 (27.0)	<.01

Abbreviations: CPAP, continuous positive airway pressure; IQR, interquartile range; SNAP II, Score for Neonatal Acute Physiology version II.

[a] Born at less than 31 weeks' gestational age.

Table 2. Comparison of Outcomes Between Preterm Infants Administered Caffeine Either Within (Early Group) or After (Late Group) the First 2 Days of Life

Variable	Caffeine Group, No. (%)		Odds Ratio (95% CI)	
	Early (n = 3806)	Late (n = 1295)	Unadjusted	Adjusted[a]
Death or BPD at 36 wk	1197 (31.5)	403 (31.1)	1.02 (0.89-1.16)	0.81 (0.67-0.98)
Death	217 (5.7)	75 (5.8)	0.98 (0.75-1.29)	0.98 (0.70-1.37)
BPD[b]				
36 wk PMA	999 (27.8)	340 (27.7)	1.00 (0.87-1.16)	0.79 (0.64-0.96)
28 d	1535 (42.2)	502 (40.2)	1.09 (0.95-1.24)	0.90 (0.74-1.09)
PDA	1503 (40.5)	576 (46.2)	0.79 (0.70-0.90)	0.74 (0.62-0.89)
PDA, , No./No. (%)				
Treated with indomethacin and ibuprofen	847/1503 (56.3)	305/576 (52.9)	1.15 (0.95-1.39)	1.17 (0.92-1.49)
Treated with surgical ligation	200/1503 (13.3)	144/576 (25.0)	0.46 (0.36-0.59)	0.58 (0.42-0.80)
ROP (≥stage 3)	229 (9.8)	95 (12.8)	0.74 (0.57-0.95)	0.78 (0.56-1.10)
NEC (≥stage 2)	240 (6.5)	78 (6.3)	1.03 (0.79-1.34)	0.88 (0.65-1.20)
Severe neurological injury[c]	432 (12.0)	167 (14.3)	0.82 (0.67-0.99)	0.80 (0.63-1.01)

Abbreviations: BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity.

[a] Adjusted for gestational age, antenatal steroid exposure, small for gestational age, site, intubated on day 2, SNAP-II score, and surfactant administration.

[b] Defined as oxygen needed.

[c] Severe neurological injury included the following: presence of parenchymal echolucency, periventricular echogenicity, or periventricular leukomalacia.

received early caffeine may have seemed ready to extubate earlier and had earlier extubation and subsequent decreased duration of mechanical ventilation. This may explain our finding of decreased BPD in the early-caffeine group. Alternatively, caffeine in extremely preterm neonates improves ventilatory drive and minute ventilation and enhances chemoreceptor sensitivity to carbon dioxide. Caffeine also has bronchodilator effects, reducing periodic breathing, increasing diaphragmatic activity, reducing hypoxic respiratory depression, and increasing urine output.[8,9] Therefore, caffeine-exposed neonates are likely to have fewer apneic spells and associated adverse outcomes. Similar to our study, in a single-center study of 140 neonates, Patel et al[13] reported that neonates who received caffeine early (<3 days) had significantly decreased incidence of death or BPD compared with those neonates who received caffeine late (≥3 days; 25.3% vs 52.6%). Dobson et al[22] also showed that neonates who received caffeine early (initial dose before 3 days of life) had significantly decreased incidence of death or BPD compared with neonates who received caffeine late (initial dose at or after 3 days of life) (27.6% vs 34.0%). In our study, BPD or death were decreased in the early-caffeine group. However, Dobson et al[22] reported that infants in the early-caffeine

Table 3. Comparison of Resource Use Between Preterm Infants Administered Caffeine Either Within (Early Group) or After (Late Group) the First 2 Days of Life

Variable	Caffeine Group, Median (IQR)		*P* Value
	Early (n = 3806)	Late (n = 1295)	
Discharged receiving oxygen, No. (%)	931 (24.5)	323 (24.9)	.73
Duration of oxygen requirement, d	9 (1-43)	8 (1-49)	.67
Duration of mechanical ventilation, d	2 (1-9)	4 (1-23)	<.01
Duration of noninvasive respiratory support, d	1 (1-5)	1 (1-5)	.02
Length of stay, d	52 (27-88)	49 (21-88)	.48
Discharged receiving caffeine, No. (%)	1386 (35.4)	475 (36.7)	.87

Abbreviation: IQR, interquartile range.

group had a higher incidence of mortality (4.5% vs 3.7%; odds ratio, 1.23; 95% CI, 1.05-1.43), a finding we did not detect in our study. Thus, the lower incidence of BPD in the early group was also similar to the Patel et al study,[13] where the rates of BPD in the early and late groups were 24% and 51%, respectively (P = .04). The decrease in the rate of BPD in neonates was possibly owing to early extubation and/or decreased duration of ventilation. The other possible reason could be that a lower percentage of infants were mechanically ventilated in the early group, indicating that the early group may have had infants who were less sick with milder respiratory immaturity.

By day 2, it is likely that physicians would have ruled out other possible causes of apnea and would be treating for true apnea of prematurity. Administration of caffeine earlier than this point would be more likely to be for prophylaxis. Neonates in the late group were sicker initially and, therefore, more likely to be ventilator dependent, with a higher incidence of cardiorespiratory morbidity including PDA. Why some infants were given early caffeine and others, late caffeine, could not be answered from our database. It is likely that because of more severe respiratory compromise and ventilator dependency, our late-group neonates were considered less likely to benefit from the early use of caffeine and, thus, were initiated at a later age. However, our findings reassure us that stable neonates who received caffeine prophylactically (or early) did not apparently experience any adverse neonatal consequences.

Our study revealed that neonates in the early group had a lower incidence of PDA compared with neonates in the late group. This finding was consistent with the findings of Patel et al.[13] Caffeine affects the signaling pathway involved in constriction of the PDA, specifically by increasing the concentration of cyclic adenosine monophosphate owing to the inhibition of cyclic nucleotide phosphodiesterase. This increase in cyclic adenosine monophosphate further releases calcium ions from the endoplasmic reticulum by binding with the ryanodine receptor, which leads to suppression of prostaglandin production and adenosine function and its activity.[23-25] Similar to the Patel et al study[13], in our study, neonates in the early group required less surgical treatment for PDA compared with neonates in the late group. A reduced need for PDA ligation was also found in the Caffeine for Apnea of Prematurity Trial,[10] with a secondary analysis that examined age of administration showing a greater effect of early administration compared with late administration, but the interaction was not significant.[14]

In a retrospective database study, Guthrie et al[26] showed that 18% of preterm neonates with NEC received caffeine in the first 10 days after birth compared with 12% of preterm neonates without NEC (P < .01). Taha et al[12] reported that early caffeine use may increase the risk for NEC in preterm infants (adjusted odds ratio, 1.4; 95% CI, 1.04-1.9; P = .03). In contrast, the Caffeine for Apnea of Prematurity Trial[10] showed no effect of caffeine started in the first 10 days after birth on NEC. Our study also did not find any difference in the incidence of NEC between the groups. In this study, we found that preterm neonates in the early group required more CPAP support on day 2 after birth in contrast with neonates in the late group, who needed more mechanical and high-frequency ventilation. This finding was similar to other studies in which preterm neonates who received caffeine early had a 1-to 2-week shorter duration of endotracheal intubation and, as a result, required a longer period of CPAP.[10,13,27]

The strengths of our study included its design as a large, multicenter national cohort study using recent data collected following standard definitions. Data entry at each center was carried out by trained data abstractors. Our analyses were adjusted for sites, all-important clinical variables, and significant variables mentioned in Table 2 in the univariate analysis. However, the limitations of this study included its retrospective observational nature, missing detailed information about racial/ethnic backgrounds, variations and inconsistency in the protocol for early caffeine use at various centers, potential variations in the maintenance dose of caffeine, and the inability to determine specific indications for caffeine use, as well as the absence of long-term neurobehavioral data from the neonates who received caffeine in the early group. Long-term neurodevelopmental outcomes of patients who received early caffeine are important to identify any potential untoward consequences.

Conclusions

Our study found that the very early initiation of caffeine does not appear to be associated with any adverse clinical outcomes. Early-caffeine therapy is associated with a reduction in the rate of death or BPD and PDA in preterm neonates. A randomized clinical trial comparing the role of early vs late caffeine therapy in very preterm infants is warranted.

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Study concept and design: Lodha, Seshia, McMillan, Barrington, Lee, Shah.
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Drafting of the manuscript: Lodha, Seshia.
Critical revision of the manuscript for important intellectual content: Lodha, Seshia, McMillan, Barrington, Yang, Shah.
Statistical analysis: Lodha, Yang.
Administrative, technical, or material support: Lodha, Seshia. Shah.
Study supervision: Lodha, Shah.

Group Information: Site investigators for the Canadian Neonatal Network include Prakesh S. Shah, MD, (director, Canadian Neonatal Network); Adele Harrison, MD, Victoria General Hospital, Victoria, British Columbia; Anne Synnes, MD, British Columbia Children's Hospital, Vancouver, British Columbia; Zenon Cieslak, MD, Royal Columbian Hospital, New Westminster, British Columbia; Todd Sorokan, MD, Surrey Memorial Hospital, Surrey, British Columbia; Wendy Yee, MD, Foothills Medical Centre, Calgary, Alberta; Khalid Aziz, MD, Royal Alexandra Hospital, Edmonton, Alberta; Zarin Kalapesi, MD, Regina General Hospital, Regina, Saskatchewan; Koravangattu Sankaran, MD, Royal University Hospital, Saskatoon, Saskatchewan; Mary Seshia, MD, Winnipeg Health Sciences Centre, Winnipeg, Manitoba; Ruben Alvaro, MD, St Boniface General Hospital, Winnipeg, Manitoba; Sandesh Shivananda, MD, Hamilton Health Sciences Centre, Hamilton, Ontario; Orlando Da Silva, MD, London Health Sciences Centre, London, Ontario; Chuks Nwaesei, MD, Windsor Regional Hospital, Windsor, Ontario; Kyong-Soon Lee, MD, Hospital for Sick Children, Toronto, Ontario; Prakesh Shah, MD, Mount Sinai Hospital, Toronto, Ontario; Michael Dunn, MD, Sunnybrook Health Sciences Centre, Toronto, Ontario; Nicole Rouvinez-Bouali, MD, Children's Hospital of Eastern Ontario and Ottawa General Hospital, Ottawa, Ontario; Kimberly Dow, MD, Kingston General Hospital, Kingston, Ontario; Lajos Kovacs, MD, Jewish General Hospital, Montréal, Québec; Keith Barrington, MD, Hôpital Sainte-Justine, Montréal, Québec; Bruno Piedboeuf, MD, Centre Hospitalier Universitaire de Québec, Sainte Foy; Patricia Riley, MD, Montréal Children's Hospital, Montréal, Québec; Daniel Faucher, MD, Royal Victoria Hospital, Montréal, Québec; Valerie Bertelle, MD, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Rody Canning, MD, Moncton Hospital, Moncton, New Brunswick; Barbara Bulleid, MD, Dr Everett Chalmers Hospital, Fredericton, New Brunswick; Cecil Ojah, MD, Saint John Regional Hospital, Saint John, New Brunswick; Wayne Andrews, MD, Janeway Children's Health and Rehabilitation Centre, St. John's, Newfoundland; Douglas McMillan, MD, IWK Health Centre, Halifax, Nova Scotia; Andrzej Kajetanowicz, MD, Cape Breton Regional Hospital, Sydney, Nova Scotia; and Shoo K. Lee, MD (chairman, Canadian Neonatal Network).

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