RESUSCITATION 135 (2019) 57–65

Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Extensive cardiopulmonary resuscitation of preterm neonates at birth and mortality and developmental outcomes

Nicole Fischer[a,1], *Amuchou Soraisham*[b,c,d,2], *Prakesh S. Shah*[e,f,3], *Anne Synnes*[g,h,4], *Yacov Rabi*[b,c,d,2], *Nalini Singhal*[b,c,d,5], *Joseph Y. Ting*[g,h,6], *Dianne Creighton*[b,c,d,7], *Deborah Dewey*[b,c,d,8], *Marilyn Ballantyne*[i,9], *Abhay Lodha*[*,b,c,d,j,10], *on behalf of the Canadian Neonatal Network™ (CNN) and the Canadian Neonatal Follow-up Network (CNFUN) Canadian Neonatal Network (CNN) Site Investigators*[11]

[a] *Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada*
[b] *Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada*
[c] *Alberta Health Services, Calgary, Alberta, Canada*
[d] *Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Canada*
[e] *Department of Pediatrics, Mount Sinai Hospital, Toronto, Ontario, Canada*
[f] *Maternal-Infant Care Research Centre, Mount Sinai Hospital, Toronto, Ontario, Canada*
[g] *B.C. Women's Hospital and Health Centre, Vancouver, British Columbia, Canada*
[h] *Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada*
[i] *Holland Bloorview Kids Rehabilitation Hospital, University of Toronto, Toronto, Ontario, Canada*
[j] *Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada*

* Corresponding author at: Department of Pediatrics & Department of Community Health Sciences, Foothills Medical Centre, Room C211, 29 Street NW, Calgary, Alberta, T2N 2T9, Canada.

E-mail addresses: nfischer@hollandbloorview.ca (N. Fischer), amuchou.soraisham@ahs.ca (A. Soraisham), asynnes@cw.bc.ca (A. Synnes), jack.rabi@ahs.ca (Y. Rabi), Nalini.Singhal@albertahealthservices.ca (N. Singhal), Jting2-02@cw.bc.ca (J.Y. Ting), diter@telusplanet.net (D. Creighton), dmdewey@ucalgary.ca (D. Dewey), MBallantyne@hollandbloorview.ca (M. Ballantyne), aklodha@ucalgary.ca (A. Lodha).

[1] Holland Bloorview Kids Rehabilitation Hospital, 150 Kilgour Road Toronto ON M4G 1R8.
[2] Department of Pediatrics, Foothills Medical Centre, Room C211, 29 Street NW, Calgary, Alberta, T2N 2T9.
[3] Departments of Paediatrics and HPME Mount Sinai Hospital and University of Toronto, CIHR Applied Research Chair in Reproductive and Child Health Services and Policy Research Director, Canadian Neonatal Network, 600 University Avenue, Room 19-231F Toronto Ontario Canada M5G 1X5.
[4] Room 1N18, BC Women's Hospital and Heath Centre, 4500 Oak St, Vancouver, BC, V6H 3V4, Canada.
[5] Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary, AB T3B 6A8.
[6] British Columbia Women's Hospital; Director, Targeted Neonatal Echocardiography Program, Clinical Investigator, BC Children's Hospital Research Institute; Clinical Associate Professor, Department of Pediatrics, The University of British Columbia. 1R46A-4480 Oak St, Vancouver, BC V6H 3V4, Canada.
[7] Department of Pediatrics, Foothills Medical Centre, Room C211, 29 Street NW, Calgary, Alberta, T2N 2T9.
[8] #397, Owerko Centre, Child Development Centre, 3820– 24th Ave NW, Calgary, AB T3B 2X9.
[9] Chief Nurse Executive, Holland Bloorview Kids Rehabilitation Hospital, 150 Kilgour Road, Toronto ON M4G 1R.
[10] Department of Pediatrics & Department of Community Health Sciences, Foothills Medical Centre, Room C211, 29 Street NW, Calgary, Alberta, T2N 2T9.
[11] A complete list of CNN and CNFUN Site Investigators appears in Appendix A.

https://doi.org/10.1016/j.resuscitation.2019.01.003
Received 14 October 2018; Received in revised form 28 November 2018; Accepted 1 January 2019

Abstract

Objective: To compare mortality and neurodevelopmental outcomes of extremely low gestational age neonates who received delivery room extensive cardiopulmonary resuscitation (DR-CPR) to those who did not require DR-CPR.

Methods: Preterm neonates born at <29 weeks' gestational age between January 2010 and September 2011 and assessed at Canadian Neonatal Follow-Up Network centers were studied. Neonates who received DR-CPR were compared to those who did not require DR-CPR using univariate and multivariable analyses. The primary outcome was a composite of mortality or any neurodevelopmental impairment at 18 to 24 months corrected age defined as the presence of any one or more of the following: cerebral palsy; Bayley-III cognitive, language, or motor composite scores <85 on any one of the components; sensorineural/mixed hearing loss or unilateral or bilateral visual impairment. Secondary outcomes were the individual components of the composite outcomes.

Results: Of the 2760 neonates born, 173 were excluded and remaining 2587 eligible neonates were included in our study. Of these 2068 had outcome data (80%) of whom 190 (9.2%) received DR-CPR. DR-CPR was independently associated with mortality or neurodevelopmental impairment (adjusted odds ratio [aOR] 1.76; 95% CI 1.21–2.55) and mortality alone (aOR1.94; 95% CI 1.33–2.83). DR-CPR was also associated with increased odds of motor impairment (aOR 2.03; 95% CI 1.28–3.23).

Conclusion: In extremely low gestational age neonates, DR-CPR was associated with higher odds of the composite outcome of mortality or neurodevelopmental impairment, mortality alone, and lower motor scores at 18 to 24 months' corrected age.

Keywords: Neonates, Neonatal resuscitation, Delivery room, Developmental outcomes, Preterm infant

Introduction

Extremely low gestational age neonates (ELGAN) can require complex medical management including delivery room resuscitation and stabilization. The neonatal resuscitation program recommends initiating cardiac compressions if the heart rate is below 60 beats per minute after correct ventilation steps have been performed.[1] Fewer than 1% of all neonates and 6–7% of preterm neonates <32 weeks' gestational age (GA) require extensive delivery room cardiopulmonary resuscitation (DR-CPR), defined as chest compressions with or without epinephrine.[1]

Previous studies regarding the association between DR-CPR and mortality and/or neurodevelopmental outcomes have shown conflicting results especially no difference versus significant difference in the outcomes.[2–7] Furthermore, many of the studies only evaluated short term neonatal outcomes.[8–13] Jankov et al. reported that neonates with birth weights <750 g who required DR-CPR had higher mortality rates but the majority of survivors were neurodevelopmentally intact.[6] Subgroup analysis of the Caffeine for Apnea of Prematurity (CAP) trial indicated that the unadjusted rates of mortality, cerebral palsy, cognitive deficits and hearing loss at 18 months corrected age (CA) increased with higher levels of resuscitation.[2] However, when adjusted for sex, GA, antenatal steroids, birth weight and multiple births, there was no significant difference between the minimal resuscitation, bag-mask ventilation, endotracheal intubation and cardiopulmonary resuscitation groups.[2] The cohort examined was assembled for a clinical trial; therefore, neonates were only included if they survived delivery room (DR) resuscitation. A report from the National Institute of Child Health and Developmental Neonatal Research Network, USA identified that DR-CPR was a prognostic indicator of morbidity and had a heavier burden of impairments at 18 months CA for survivors.[7] A systematic review of ten studies identified a higher odds of mortality and intraventricular hemorrhage (IVH) with DR-CPR but no difference in the odds of neurodevelopmental impairment (NDI).[14] However, only a limited number of studies examined long-term outcomes and the reported studies had high rates of attrition.[14]

Preterm children are known to be at an increased risk of NDI with motor impairments such as cerebral palsy and non-cerebral palsy motor impairments compared to term neonates[15]; however, it is not clear from previous studies whether DR-CPR is an additional risk factor for NDI or motor impairments in ELGAN. We hypothesized that preterm neonates requiring extensive DR-CPR at birth will have a higher rate of mortality or adverse neurodevelopmental outcomes at 18–24 months' CA than neonates who did not require DR-CPR because of the effects of hypoxia and hypo-perfusion on brain development and subsequent brain injury or mortality. Thus, the objective of this study was to compare mortality or neurodevelopmental outcomes of preterm neonates born in Canadian NICUs at <29 weeks' GA who received DR-CPR (with or without epinephrine) to those who did not require DR-CPR.

Patients and methods

In this retrospective cohort study, inborn neonates who were born between January 1, 2010 and September 30, 2011 at <29 weeks' GA in NICUs affiliated with the Canadian Neonatal Network (CNN) and completed a follow-up assessment at 18–24 months' CA at a Canadian Neonatal Follow-up Network (CNFUN) clinic were included. The CNN included 28 tertiary NICUs in Canada who collected maternal and neonatal data for all NICU admissions. All 26 CNFUN clinics provided follow-up data at 18–24 months' CA for this study. The data for neonates admitted to the two additional CNN NICUs without a neonatal follow-up program were not included in this study. The study population covered ~90% of preterm neonates born at <29 weeks' GA in Canada. We excluded neonates with major congenital or chromosomal anomalies, those who were moribund at delivery or decided to have a planned palliative care before delivery. Those lost to follow-up were also excluded.

Data collection and ethics

Data abstractors collected data at individual centers and data were transmitted electronically to the coordinating center at Mount Sinai Hospital in Toronto, Ontario, Canada. Data collection during the initial hospitalization was approved by individual hospital research ethics boards or local quality improvement committees and

parental consent for data collection at a follow-up visit was obtained where required by research ethics boards. All centers used the standard definitions of variables as defined by the CNN and CNFUN data abstractor's manual.[16,17] Data collection in the CNN was reported to be highly reliable and internally consistent.[18] This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary and steering committees of both networks.

Definitions

Extensive DR-CPR was defined as chest compressions for at least 30 s with or without the use of epinephrine during delivery room resuscitation. Neonates were divided into two groups: those that did and did not receive DR-CPR. Gestational age was defined as the best obstetric estimate based on early antenatal ultrasound, obstetric examination, and obstetric history. Resuscitation details for each neonate were recorded from maternal and neonatal charts. All support received by the neonate in the first 30 min after birth during the initial resuscitation was recorded. Support included the following: no resuscitation needed, stimulation, suction, free-flow oxygen, continuous positive airway pressure, positive pressure ventilation via bag and mask or endotracheal tube, chest compressions for >30 s, and endotracheal or intravenous administration of epinephrine. The severity of IVH was classified as per Papile's classification system.[19] Severe neurological injury was defined by the presence of IVH ≥grade 3 or persistent periventricular echogenicity.[16] Bronchopulmonary dysplasia (BPD) was diagnosed based on oxygen dependence and/or respiratory support at 36 weeks post menstrual age[20] or at the time of transfer to a level 2 hospital if discharged earlier. The severity of necrotising enterocolitis was based on modified Bell's criteria (≥stage 2).[21] Severity of illness was measured using the Score for Neonatal Acute Physiology, version II (SNAP-II) as described by Richardson et al.[22]

Neurodevelopmental assessment

In a multidisciplinary CNFUN follow-up clinic, the neonates were evaluated for neurodevelopmental outcomes at 18 to 24 months' CA as previously described.[17] Cerebral palsy was diagnosed according to Rosenbaum et al.[23] and severity classified using the Gross Motor Function Classification System (GMFCS).[24] Trained assessors at each CNFUN center used the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III)[25] for their developmental assessment, which included cognitive, motor, and language composite scores. The Bayley-III scores were computed relative to a standardized mean (±standard deviation [SD]) of 100 ± 15, with higher scores indicating better performance. Hearing assessment results and the need for hearing aids or cochlear implants were obtained from patient histories. Ophthalmology follow-up for retinopathy of prematurity (ROP) and visual status was documented. If the vision history was unknown, a small or scarred eye, sustained sensory nystagmus, or lack of response to a 1 cm object on a white background from a distance of 30 cm were defined as visual impairment.

Outcome measures

The primary outcome for this study is the composite of mortality or NDI at 18 to 24 months' CA. All mortality (Deaths in NICU and after discharge but before follow-up age) from births to 18 to 24 months CA were included in the study. This outcome was selected because neonates who went to a follow-up appointment but died before the neurodevelopmental assessment at 18–24 months' CA could not be classified as having NDI. NDI was defined as any cerebral palsy (GMFCS ≥1), Bayley-III score <85 on one or more of the cognitive, motor or language composite scores, sensorineural or mixed hearing impairment or unilateral or bilateral visual impairment. Children who could not be tested using the Bayley-III or with a score <85 on the Bayley-III General Adaptive Composite score questionnaire or deemed to have developmental delay were also included.

The secondary outcomes include significant neurodevelopmental impairment (sNDI), mortality, a Bayley-III score of <85 on any one of the components (cognitive, language, motor), sensorineural or mixed hearing loss, or visual impairment. sNDI was defined as the presence of one or more of the following: cerebral palsy with GMFCS ≥3, Bayley-III cognitive, language or motor composite score <70, hearing impairment requiring hearing aids or cochlear implant, or bilateral visual impairment.[17]

Data analyses

Maternal and neonatal characteristics as well as neonatal outcomes were described according to DR-CPR group. Frequency (percentage), mean (standard deviation) or median (interquartile range) were reported. Significance between DR-CPR and No DR-CPR groups was assessed by Pearson's Chi-square test for categorical variables and student t-test or Wilcoxon rank test for continuous variables. Multivariable logistic regression analyses were conducted for primary and secondary outcomes. For secondary outcomes (except mortality) only neonates with a follow-up assessment were included. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated after adjusting for potential confounding variables: receipt of antenatal corticosteroids, sex, GA, small for gestational age (SGA, birth weight <10 centile), multiple gestations and outborn status. All analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC) with a significance level of 0.05.

Results

A total of 2760 preterm neonates of <29 weeks' GA were admitted to the 28 participating NICUs during the study period. One hundred and seventy-three neonates were excluded as they had major congenital abnormalities (n = 119), missing data (n = 7) or were moribund at birth (n = 47). Of the 2587 remaining eligible neonates, 2068 neonates with follow-up data (80% follow-up rate) were included. Of the included neonates, 190 (9.2%) received DR-CPR (Fig. 1). Of 190 neonates in the DR-CPR group, 125 neonates received chest compression only, 9 neonates received epinephrine alone and 56 neonates received both chest compression and epinephrine.

In Table 1, the demographic characteristics of the study population and the group without follow-up data were compared. The neonates

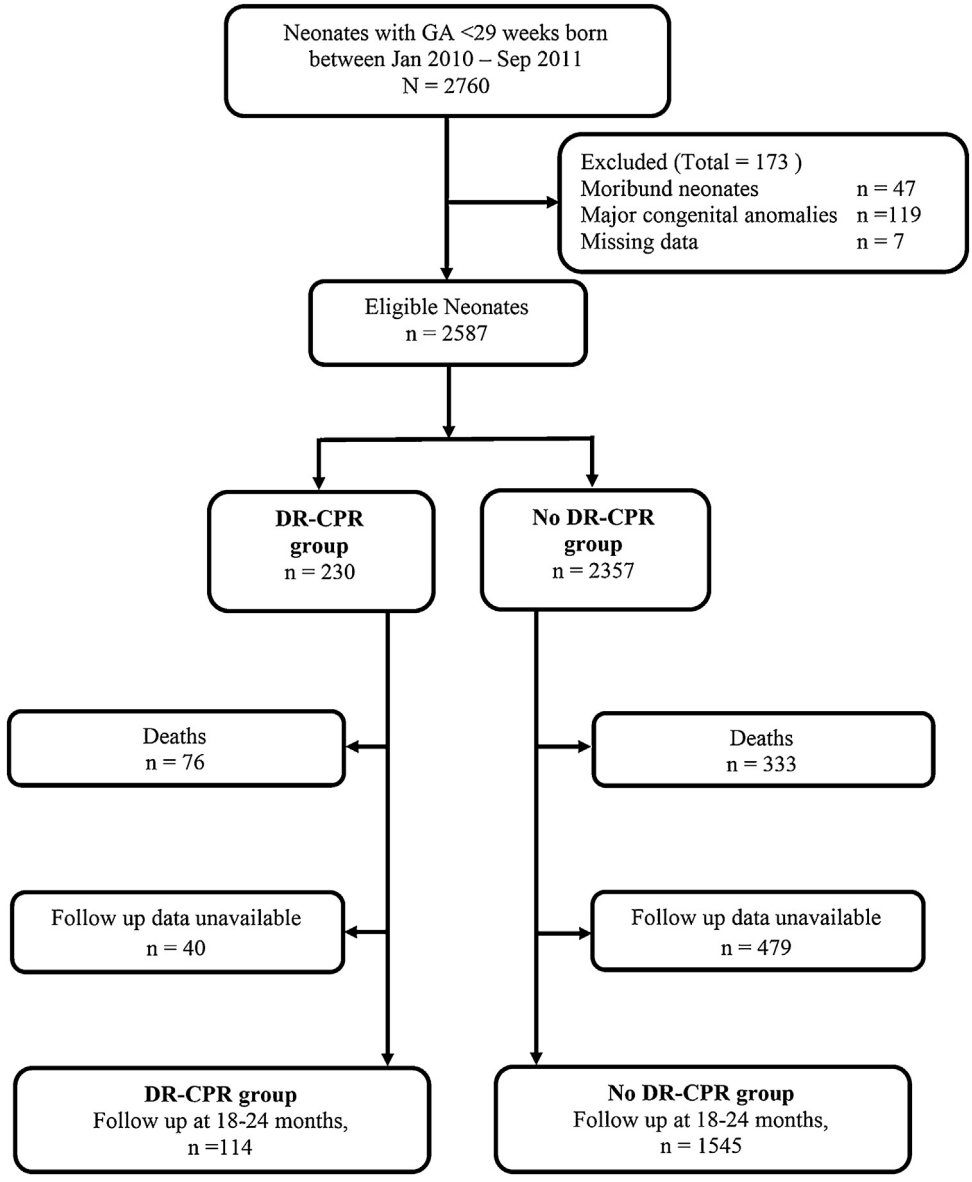

Fig. 1 – Flow diagram of the study cohort.

that were lost to follow-up were born at a higher GA, weighed more, and had lower SNAP-II scores in first 12 h of admission.

The variability of the maternal and neonatal characteristics in the DR-CPR and No DR-CPR groups was assessed in Table 2. Neonates who did not receive DR-CPR were more likely to be born to mothers with hypertension or who received antenatal corticosteroids. Neonates who received DR-CPR were of lower birth weight and GA on average and had lower Apgar scores at 1, 5 and 10 min. In addition, the neonates who received DR-CPR had significantly higher SNAP-II scores than neonates in the No DR-CPR group.

The rates of neonatal outcomes in the DR-CPR and No DR-CPR groups were compared in Table 3. Neonates who received DR-CPR had higher rates of severe brain injury, seizures, BPD, ROP ≥stage 2 or treated ROP and mortality than neonates who did not receive DR-CPR. The number of neonates who died in NICUs were 76 and 312 in the DR-CPR group and No DR-CPR group respectively. In addition to this, a total of 21 neonates died after hospital discharge from the hospitals in the No DR-CPR group compared to zero in the DR-CPR group. The median (interquartile range) age of death in the DR-CPR group and No DR-CPR group were 3 (1,15) and 9 (3,25) days respectively.

The association between DR-CPR and neurodevelopmental outcomes at 18–24 months' CA is reported in Table 4. After adjustment for GA, antenatal corticosteroids, sex, SGA, multiple gestations, and outborn status, DR-CPR was associated with increased odds of composite outcome of mortality or NDI (OR:1.76; 95%CI: 1.21–2.55) and mortality alone (OR:1.94; 95%CI: 1.33–2.83). The primary outcome varied with the type of DR-CPR (epinephrine only group versus chest compression group only versus epinephrine with chest compression group). Both chest compression only (OR:1.70; 95%CI: 1.10–2.65) and epinephrine with chest compression (OR:2.39; 95%CI: 1.12–5.08) were associated with an increased risk of the composite outcome of mortality or NDI, whereas there was no significant association for the group receiving epinephrine alone (OR:0.75; 95%CI: 0.19–3.02). In addition, among those who were assessed at 18–24 months' CA, DR-CPR was associated with an

Table 1 – Demographic characteristics of study population and neonates lost to follow-up.

	Lost to follow-up N = 519	Study population N = 2068	p-Value
Neonatal characteristics			
Birth weight (grams), mean (SD)	1010 (236)	902 (239)	<0.01
Gestational age (weeks), mean (SD)	26.7 (1.3)	26.1 (1.5)	<0.01
≤24 weeks, n (%)	33 (6.4)	353 (17.1)	
25–28 weeks, n (%)	483 (93.6)	1715 (82.9)	
Male, n (%)	283 (54.7)	1108 (53.6)	0.65
Small for gestational age, n (%)	31 (6.0)	174 (8.4)	0.07
Multiple gestations, n (%)	124 (24.0)	565 (27.3)	0.13
Surfactant, n (%)	366 (70.5)	1667 (80.6)	<0.01
SNAP-II score, median (IQR)	9 (5, 15)	14 (9, 24)	<0.01
Outborn, n (%)	138 (26.7)	319 (15.4)	<0.01
DR-CPR, n (%)	40 (7.7)	190 (9.2)	0.29

The denominator for calculating the percentage value is not always the same as the total number of neonates in the groups due to missing cases.
Abbreviation: DR-CPR, delivery room cardiopulmonary resuscitation; IQR, interquartile range; N, number in group; SD, standard deviation; n, number in category; SNAP-II; Score for Neonatal Acute Physiology version II.

Table 2 – Demographic characteristics of DR-CPR and No DR-CPR groups.

	DR-CPR N = 190	No DR-CPR N = 1878	p-Value
Maternal characteristics			
Maternal age (years), mean (SD)	30.2 (6.2)	30.6 (5.9)	0.45
College or above education[a], n (%)	60 (67.0)	919 (64.5)	0.25
Caucasian[a], n (%)	67 (67.0)	889 (67.7)	0.89
Social welfare[a], n (%)	14 (14.0)	131 (10.1)	0.21
Primigravida, n (%)	59 (31.6)	686 (36.8)	0.15
Hypertension, n (%)	21 (11.5)	316 (17.2)	0.05
Diabetes, n (%)	13 (7.2)	143 (8.0)	0.71
Antenatal steroids, n (%)	131 (74.9)	1642 (89.3)	<0.01
Rupture of membrane >24 h, n (%)	41 (22.9)	401 (21.9)	0.77
Cesarean section, n (%)	99 (52.1)	1066 (57.0)	0.19
Neonatal characteristics			
Birth weight (grams), mean (SD)	832 (238)	909 (238)	<0.01
Gestational age (weeks), mean (SD)	25.4 (1.7)	26.1 (1.5)	<0.01
≤24 weeks, n (%)	55 (28.9)	298 (15.9)	<0.01
25–28 weeks, n (%)	135 (71.1)	1580 (84.1)	
Male, n (%)	111 (58.4)	997 (53.1)	0.16
Small for gestational age, n (%)	14 (7.4)	160 (8.5)	0.60
Multiple gestations, n (%)	39 (20.5)	526 (28.0)	0.03
Apgar score at 1 min, median (IQR)	1 (1, 2)	5 (3, 6)	<0.01
Apgar score at 5 min, median (IQR)	4 (2, 6)	7 (6, 8)	<0.01
Apgar score at 10 min, median (IQR)	6 (4, 7)	7 (7, 8)	<0.01
Surfactant, n (%)	166 (87.4)	1501 (79.9)	0.01
SNAP-II score, median (IQR)	24 (14, 35)	14 (9, 22)	<0.01
Outborn, n (%)	67 (35.3)	252 (13.4)	<0.01

Abbreviations: DR-CPR, delivery room cardiopulmonary resuscitation; IQR, interquartile range; N, number in group; n, number in category; SD, standard deviation; SNAP-II, Score for Neonatal Acute Physiology, version II.
*The denominator for calculating the percentage value is not always the same as the total number of infants in the groups due to missing cases.
[a] Only for infants who had data available.

increased adjusted odds of a Bayley-III motor composite score of <85 but was not associated with cerebral palsy, or Bayley-III language or cognitive scores.

Discussion

In this large, multi-center, population-based study of ELGAN, the rate of DR-CPR was 9.2%, in contrast to other studies that had variable rates of DR-CPR ranges from 4% to 15%.[2–7] DR-CPR was associated with increased adjusted odds of both the composite outcome of mortality or NDI and mortality alone. We also identified that neonates who received DR-CPR had higher odds of a Bayley-III motor score <85 than neonates who did not require DR-CPR.

Similar to our study, previous work reported increased odds of adverse neonatal outcomes following DR-CPR, including increased mortality and severe neurological injury. Deulofeut et al.

Table 3 – Comparison of neonatal outcomes between DR-CPR and No DR-CPR groups.

Outcomes	DR-CPR N = 190	No DR-CPR N = 1878	p-Value
Seizure, n (%)	17 (9.0)	97 (5.2)	0.03
Severe neurological injury,[b] n (%)	49 (28.3)	264 (14.5)	<0.01
Bronchopulmonary dysplasia,[c] n (%)[a]	72 (61.0)	725 (45.7)	<0.01
Intestinal perforation, n (%)	12 (6.6)	98 (5.3)	0.47
Necrotizing enterocolitis ≥ stage 2, n (%)[a]	21 (11.1)	173 (9.2)	0.39
Retinopathy of prematurity >stage 2 or treated, n (%)[a]	25 (23.4)	192 (15.0)	0.02
Patent ductus arteriosus required medical or surgical treatment, n (%)	82 (43.2)	827 (44.0)	0.82
Early-onset sepsis, n (%)	6 (3.2)	35 (1.9)	0.22
Nosocomial sepsis, n (%)	54 (28.4)	511 (27.2)	0.72

Abbreviations: DR-CPR, delivery room cardiopulmonary resuscitation; N, number in group; n, number in category.
[a] The denominator for calculating the percentage value is not always the same as the total number of infants in the groups due to missing cases.
[b] Severe neurological injury is defined as IVH ≥ grade 3 and/or persistent periventricular echogenicity.
[c] Bronchopulmonary dysplasia among survivors.

Table 4 – Comparison of neurodevelopmental outcomes at 18 to 24 months' CA.

Outcomes of included neonates	n (%)		aOR[a] (95% CI)
	DR-CPR N = 190	No DR-CPR N = 1878	
Death	76 (40.0)	333 (17.7)	1.94 (1.33, 2.83)
Death or NDI	143 (75.3)	1028 (54.7)	1.76 (1.21, 2.55)
Outcomes of assessed neonates	DR-CPR N = 114	No DR-CPR N = 1545	aOR[a] (95%CI)
NDI	67 (58.8)	695 (45.1)	1.47 (0.97, 2.22)
sNDI	25 (21.9)	256 (16.6)	1.15 (0.70, 1.88)
Cerebral palsy	11 (9.8)	88 (5.8)	1.57 (0.79, 3.09)
Bayley-III Cognitive Composite score <85	23 (22.1)	209 (14.5)	1.45 (0.87, 2.43)
Bayley-III Motor Composite score <85	35 (35.7)	272 (19.6)	2.03 (1.28, 3.23)
Bayley-III Language Composite score <85	41 (41.8)	497 (35.5)	1.05 (0.67, 1.65)
Hearing impairment	13 (12.2)	112 (7.7)	1.46 (0.76, 2.81)
Visual impairment	3 (2.9)	23 (1.6)	NA

Abbreviations: n, number in category; DR-CPR, delivery room cardiopulmonary resuscitation; N, number in group; aOR, adjusted odds ratio; CI, confidence interval; NDI, neurodevelopmental impairment; sNDI, significant neurodevelopmental impairment; NA, not applicable.
[a] Adjusted for GA, antenatal corticosteroids, sex, SGA, multiple gestations, and outborn.

reported that neonates who received DR-CPR (n = 53) had higher odds of mortality (odds ratio [OR] 14.03 [95%CI 1.49,1.38]) and severe neurological injury (OR 3.52 [95%CI 1.50,11.74]) than neonates who did not receive DR-CPR.[3] In a single centre study, Shah et al. also reported that neonates born <32 weeks' GA and received DR-CPR had a higher risk of combined adverse outcome of mortality or severe neurological injury than neonates who did not require DR-CPR (58% versus 37%; p = 0.04).[12] Wyckoff et al. who included 1333 neonates in their DR-CPR group (out of a total of 8685 neonates) reported that the risk of IVH grade 3 and 4 (OR 1.47 [95%CI 1.23,1.74]) and mortality by 120 days after birth (OR 2.22 [95%CI 1.93, 2.57]) were increased in neonates who received DR-CPR.[7]They included neonates born between January 1996 to December 2002[7] whereas our study included neonates born between January 1, 2010 and September 30, 2011. Arnon et al. reported that neonates who received DR-CPR had a higher risk of mortality (70.9% versus 34.8%, p < 0.0001), IVH grades 3 and 4, (39.6% versus 25.2%, p < 0.0001) and periventricular leukomalacia (20.3% versus 11.2%, p = 0.001) than those who did not require DR-CPR.[8] A report from the Vermont Oxford Network Database found that neonates of 501 to 1500 grams birth weight who received DR-CPR had an increased risk grades 3 and 4 IVH and mortality.[4] The rate of death or NDI (54.7%) was also high in children who did not receive CPR in the delivery room possibly because of lower receipt of maternal antenatal steroids, extremely low gestational age at birth, and also because we included minor neurodevelopmental impairments in NDI criteria.

However, there are also several previous studies that reported different results for DR-CPR, particularly for extremely low birth weight neonates. For example, the Vermont Oxford Network reported that neonates with a birth weight of 401–500 grams who received DR-CPR had a higher survival rate than neonates who did not require DR-CPR, which the authors believed was because of aggressive resuscitation and ventilation of neonates with a higher chance of survival.[4] Furthermore, Sanchez-Torres et al. reported no significant difference in the risk of mortality and neurological morbidities between DR-CPR and No DR-CPR groups.[11] In contrast, Campbell et al. reported that 15 of 91 (16.5%) neonates born with a birth weight of ≤750 grams received DR-CPR, and none of them survived to discharge.[26] The impact of DR-CPR on the survival of extremely low birth weight neonates is not surprising because they are fragile neonates who may not survive regardless of whether or not they receive DR-CPR. If they do survive,

prolonged hypoxemia, lack of perfusion, acidemia (including both lactate and elevated levels of CO_2) can negatively affect multiple organ systems, which may result in reduced survival.

In our study, the increased rates of severe neurological injury in those who received DR-CPR could have multiple possible mechanisms. Ischemia-reperfusion, entry of epinephrine into circulation after resuscitation resulting in altered blood pressure from hypotension to sudden hypertension, lack of protective effects of antenatal steroids, and lower GA are all possible mechanisms for increased severe neurological injury in our cohort.

Neonates in our study who received DR-CPR showed higher adjusted odds of composite outcomes of mortality or NDI and risk of motor impairments than the No DR-CPR neonates. Deulofeut et al. identified that neonates who required DR-CPR had lower Mental Developmental Index (67.7 ± 18.3 versus 81.3 ± 17.7; $p = 0.006$) and Psychomotor Developmental Index (74.4 ± 19.9 versus 85.1 ± 17.2; $p = 0.027$) scores than neonates who did not require DR-CPR.[3] Wyckoff et al. reported an increased rate of composite outcome of mortality or NDI (OR 1.70 [95% CI 1.46, 1.99]) in DR-CPR neonates when compared to No DR-CPR neonates.[7] They also reported that extremely low birth weight neonates who survived DR-CPR had a higher risk of motor impairments with cerebral palsy and bilateral deafness.[7] Jankov et al. reported that in their cohort, six neonates (26%) of $\leq$750 grams birth weight had moderate to profound gross motor deficits in the DR-CPR group but no difference in the risk of NDI at 15–72 months.[6] In contrast, other studies did not show any difference in NDI or motor impairments in neonates who received DR-CPR compared to neonates who did not receive DR-CPR.[2,27] We believe that the higher risk of composite of mortality or NDI in DR-CPR neonates in our study is possibly due to severe neurological injury, increased illness severity scores at birth and higher rates of outborn status[28] There are some preventable antenatal factors including lower receipt of antenatal steroids and increased outborn delivery in the DR-CPR group. These factors can be prevented with better obstetric care and improved neonatal resuscitation of extremely low gestational age neonates in the delivery room.

Our study has several strengths. It is a large multi-center study with detailed and meticulous data on neonates admitted to NICUs across Canada. Uniform definitions for DR-CPR and neurodevelopmental outcomes were utilized as the data were extracted from a national database[17]. Furthermore, standardized tests were used to perform the developmental assessments. Our study cohort has a large number of neonates born in recent years, lower attrition rate, and better follow-up rate than other studies that compared long-term outcomes between DR-CPR and No DR-CPR groups.[3,4,6] There are several changes that have happened in the resuscitation of extremely low gestational age neonates in the last two decades and it is important to review contemporary data with changing practices. However, our study does have some limitations. First, ours is a retrospective study which introduces risk of bias as the assessors were not blinded to the infants' neonatal course. Second, there is some missing information from lack of complete follow-up, which may introduce attrition bias. However, the group lost to follow-up had a slightly higher mean gestational age and birth weight and thus, we may have underestimated the risk of DR-CPR. Finally, the neonates included in our study were only followed up to 18–24 months' CA, and their long-term risk of NDI at 3 and 5 years, which is not known, would be of significant interest.

Conclusions

In conclusion, DR-CPR for neonates born at <29 weeks' GA was associated with adverse composite outcome of mortality or NDI, mortality alone, and lower motor scores at 18–24 months' CA. The results of this study will be useful for counseling the parents in NICUs regarding prognostication of neurodevelopmental outcomes in ELGAN who receive DR-CPR. These results do not indicate that neonates who did not require DR-CPR do not require neurodevelopmental follow-up as they also have high rates of NDI. Follow-up strategies to prevent or reduce the burden of morbidities could include; encouraging positive early parent-infant relationship, improving the home environment through parental education, providing supports for parental coping, offering infant developmental stimulation and providing a regular multidisciplinary follow-up program. Studies with longer term follow-up are required to determine the risk of learning disabilities and attention difficulties in these children as they reach school age.

Funding source

Although no specific funding has been received for this study, organizational support for the Canadian Neonatal Network was provided by the Maternal-Infant Care Research Centre (MiCare) at Mount Sinai Hospital in Toronto, Ontario, Canada. MiCare and the Canadian Neonatal Follow-Up Network are supported by a Canadian Institutes of Health Research (CIHR) Team Grant (CTP 87518), the Ontario Ministry of Health, and in-kind support from Mount Sinai Hospital. Dr. Shah holds an Applied Research Chair in Reproductive and Child Health Services and Policy Research awarded by the CIHR (APR-126340). The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest

None.

Acknowledgments

The authors would like to thank the data abstractors from the Canadian Neonatal Network (CNN) and all of the staff at the CNN coordinating center for providing organizational support. We would like to acknowledge Sarah Hutchinson, PhD, from the Maternal-Infant Care Research Center (MiCare) for her editorial support in the preparation of this manuscript.

Appendix A. Network Investigators

Canadian Neonatal Network (CNN) Site Investigators

Prakesh S Shah, MD, MSc (Director, Canadian Neonatal Network and site investigator), Mount Sinai Hospital, Toronto, Ontario; Jaideep Kanungo, MD, Victoria General Hospital, Victoria, British Columbia; Joseph Ting, MD, B.C. Women's Hospital and Health Centre,

Vancouver, British Columbia; Wendy Yee, MD, Foothills Medical Centre, Calgary, Alberta; Jennifer Toye, MD, Royal Alexandra Hospital, Edmonton, Alberta; Carlos Fajardo, MD, Alberta Children's Hospital, Calgary, Alberta; Zarin Kalapesi, MD, Regina General Hospital, Regina, Saskatchewan; Koravangattu Sankaran, MD, MBBS, and Sibasis Daspal, MD, Royal University Hospital, Saskatoon, Saskatchewan; Mary Seshia, MBChB, Winnipeg Health Sciences Centre, Winnipeg, Manitoba; Ruben Alvaro, MD, St. Boniface General Hospital, Winnipeg, Manitoba; Amit Mukerji, MD, Hamilton Health Sciences Centre, Hamilton, Ontario; Orlando Da Silva, MD, MSc, London Health Sciences Centre, London, Ontario; Chuks Nwaesei, MD, Windsor Regional Hospital, Windsor, Ontario; Kyong-Soon Lee, MD, MSc, Hospital for Sick Children, Toronto, Ontario; Michael Dunn, MD, Sunnybrook Health Sciences Centre, Toronto, Ontario; Brigitte Lemyre, MD, Children's Hospital of Eastern Ontario and Ottawa General Hospital, Ottawa, Ontario; Kimberly Dow, MD, Kingston General Hospital, Kingston, Ontario; Ermelinda Pelausa, MD, Jewish General Hospital, Montréal, Québec; Anie Lapoint, MD, Hôpital Sainte-Justine, Montréal, Québec; Christine Drolet, MD, and Bruno Piedboeuf, MD, Centre Hospitalier Universitaire de Québec, Sainte Foy, Québec; Martine Claveau, MSc, LLM, NNP, and Marc Beltempo, MD, Montreal Children's Hospital at McGill University Health Centre, Montréal, Québec; Valerie Bertelle, MD, and Edith Masse, MD, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Roderick Canning, MD, Moncton Hospital, Moncton, New Brunswick; Hala Makary, MD, Dr. Everett Chalmers Hospital, Fredericton, New Brunswick; Cecil Ojah, MBBS, and Luis Monterrosa, MD, Saint John Regional Hospital, Saint John, New Brunswick; Julie Emberley, MD, Janeway Children's Health and Rehabilitation Centre, St. John's, Newfoundland; Jehier Afifi, MB BCh, MSc, IWK Health Centre, Halifax, Nova Scotia; Andrzej Kajetanowicz, MD, Cape Breton Regional Hospital, Sydney, Nova Scotia; Shoo K Lee, MBBS, PhD (Chairman, Canadian Neonatal Network), Mount Sinai Hospital, Toronto, Ontario.

Canadian Neonatal Follow-Up Network (CNFUN) Investigators: Thevanisha Pillay, MD, Victoria General Hospital, Victoria, British Columbia; Anne Synnes, MDCM, MHSC (Director, CNFUN), B. C. Women's Hospital and Health Centre, Vancouver, British Columbia; Reg Sauvé, MD, MPh, Leonora Hendson MBBCH, MSc, Alberta's Children's Hospital, Foothills Medical Centre, Calgary, Alberta; Amber Reichert, MD, Glenrose Rehabilitation Hospital, Edmonton, Alberta; Jaya Bodani, MD, Regina General Hospital, Regina, Saskatchewan; Koravangattu Sankaran, MD, Royal University Hospital, Saskatoon, Saskatchewan; Diane Moddemann, MD, Winnipeg Health Sciences Centre, St. Boniface General Hospital, Winnipeg, Manitoba; Chuks Nwaesei, MD, Windsor Regional Hospital, Windsor, Ontario; Thierry Daboval, MD, Children's Hospital of Eastern Ontario, Ottawa, Ontario; Kimberly Dow, Kingston General Hospital, Kingston, Ontario; David Lee, MD and Dr. Kevin Coughlin, Children's Hospital London Health Sciences Centre, London, Ontario; Linh Ly, MD, Hospital for Sick Children, Toronto, Ontario; Edmond Kelly, MD, Mount Sinai Hospital, Toronto, Ontario; Saroj Saigal, MD, Hamilton Health Sciences Centre, Hamilton, Ontario; Paige Church, MD, Sunnybrook Health Sciences Centre, Toronto, Ontario; Ermelinda Pelausa, MD, Jewish General Hospital, Montréal, Québec; Patricia Riley, MD, Montréal Children's Hospital, Royal Victoria Hospital, Montréal, Québec; Thuy Mai Luu, MDCM, Francine Lefebvre, Centre Hospitalier Universitaire Sainte-Justine, Montréal, Québec; Charlotte Demers, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Sylvie Bélanger, MD, Centre Hospitalier Universitaire de Québec, Québec City, Québec; Roderick Canning, MD, Moncton Hospital, Moncton, New Brunswick; Luis Monterrosa, MD, Saint John Regional Hospital, Saint John, New Brunswick; Hala Makary, MD, Dr. Everett Chalmers Hospital, Fredericton, New Brunswick; Jehier Afifi, MD, Michael Vincer, MD, IWK Health Centre, Halifax, Nova Scotia; Phil Murphy, Charles Janeway Children's Health and Rehabilitation Centre, St. John's, Newfoundland.

REFERENCES

1. Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal resuscitation: American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics 2010;126:e1400–13 [Erratum appears in Pediatrics. 2011 Jul;128 (1):176].
2. DeMauro SB, Roberts RS, Davis P, et al. Impact of delivery room resuscitation on outcomes up to 18 months in very low birth weight infants. J Pediatr 2011;159:546–50 e1.
3. Deulofeut R, Sola A, Lee B, Rogido M. Delivery room cardiopulmonary resucitation of very preterm infant is associated with adverse short- and long-term outcomes. An Pediatr (Barc) 2007;66:31–7.
4. Finer NN, Tarin T, Vaucher YE, Barrington K, Bejar R. Intact survival in extremely low birth weight infants after delivery room resuscitation. Pediatrics 1999;104:e40.
5. Francis P, Casiro O. Neurodevelopmental outcome of very low birth weight children requiring chest compressions immediate after birth. Pediatr Res 1997;41:196A.
6. Jankov RP, Asztalos EV, Skidmore MB. Favourable neurological outcomes following delivery room cardiopulmonary resuscitation of infants < or = 750 g at birth. J Paediatr Child Health 2000;36:19–122.
7. Wyckoff MH, Salhab WA, Heyne RJ, et al. Outcome of extremely low birth weight infants who received delivery room cardiopulmonary resuscitation. J Pediatr 2012;160:239–44 e2.
8. Arnon S, Dolfin T, Reichman B, et al. Delivery room resuscitation and adverse outcomes among very low birth weight preterm infants. J Perinatol 2017;37:1010–6.
9. Finer NN, Horbar JD, Carpenter JH. Cardiopulmonary resuscitation in the very low birth weight infant: the Vermont Oxford Network experience. Pediatrics 1999;104:428–34.
10. Handley SC, Sun Y, Wyckoff MH, Lee HC. Outcomes of extremely preterm infants after delivery room cardiopulmonary resuscitation in a population-based cohort. J Perinatol 2015;35:379–83.
11. Sanchez-Torres AM, Garcia-Alix A, Cabanas F, et al. Impact of cardiopulmonary resuscitation on extremely low birth weight infants. An Pediatr (Barc) 2007;66:38–44.
12. Shah PS, Shah P, Tai KF. Chest compression and/or epinephrine at birth for preterm infants <32 weeks gestational age: matched cohort study of neonatal outcomes. J Perinatol 2009;29:693–7.
13. Sims DG, Heal CA, Bartle SM. Use of adrenaline and atropine in neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 199470: F3-9; discussion F-10.
14. Shah PS. Extensive cardiopulmonary resuscitation for VLBW and ELBW infants: a systematic review and meta-analyses. J Perinatol 2009;29:655–61.
15. Spittle AJ, Orton J. Cerebral palsy and developmental coordination disorder in children born preterm. Semin Fetal Neonatal Med 2014;19:84–9.
16. Abstractor's Manual-The Canadian Neonatal Network. Toronto The Canadian Neonatal Network; 2011. http://wwwcanadianneonatalnetworkorg/Portal/LinkClickaspx?fileticket=U4anC.
17. Synnes A, Luu TM, Moddemann D, et al. Determinants of developmental outcomes in a very preterm Canadian cohort. Arch Dis Child Fetal Neonatal Ed 2017102: F235-F4.

18. Shah PS, Seidlitz W, Chan P, et al. Internal audit of the Canadian neonatal network data collection system. Am J Perinatol 2017;34:1241–9.
19. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529–34.
20. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527–32.
21. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33:179–201 Review.
22. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. J Pediatr 2001;138:92–100.
23. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007;109:8–14.
24. Palisano R, Rosenbaum P, Walter S. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214–23.
25. Bayley N. Manual for the Bayley Scales of Infant and Toddler Development. 3rd. San Antonio, TX: The Psychological Corporation; 2006.
26. Campbell ME, Byrne PJ. Cardiopulmonary resuscitation and epinephrine infusion in extremely low birth weight infants in the neonatal intensive care unit. J Perinatol 2004;24:691–5.
27. Davis DJ. How aggressive should delivery room cardiopulmonary resuscitation be for extremely low birth weight neonates. Pediatrics 1993;92:447–50.
28. Amer R, Moddemann D, Seshia M, et al. Neurodevelopmental outcomes of infants born at <29 weeks of gestation admitted to Canadian neonatal intensive care units based on location of birth. J Pediatr 2018;196:31–7.