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ORIGINAL ARTICLE

Delivery room resuscitation and adverse outcomes among very low birth weight preterm infants

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OBJECTIVE: To evaluate risk factors and impact of delivery room cardiopulmonary resuscitation (DR-CPR) on very low birth weight (VLBW) preterm infants.

STUDY DESIGN: A national, population-based, observational study evaluating risk factors and short-term neonatal outcomes associated with DR-CPR among VLBW, extremely preterm infants (EPIs, 24 to 27 weeks' gestation) and very preterm infants (VPI, 28 to 31 weeks' gestation) born in 1995 to 2010.

RESULTS: Among 17 564 VLBW infants, 636 (3.6%) required DR-CPR. In the group of 6478 EPI, 412 (6.4%) received DR-CPR compared with 224 of 11 086 infants (2.0%) in the VPI group. EPI who underwent DR-CPR had higher odds ratios (ORs (95% confidence interval)) for mortality compared to EPI not requiring DR-CPR (OR 3.32 (2.58, 4.29)), grades 3 to 4 intraventricular hemorrhage (IVH) (OR 1.59 (1.20, 2.10)) and periventricular leukomalacia (OR 1.81 (1.17, 2.82)). DR-CPR among VPI was associated with higher ORs for mortality (OR 4.99 (3.59, 6.94)), early sepsis (OR 2.07 (1.05, 4.09)), grades 3 to 4 IVH (OR 3.74 (2.55, 5.50)) and grades 3 to 4 retinopathy of prematurity (ROP) (OR 2.53 (1.18, 5.41)) compared to VPI not requiring DR-CPR. Only 11% of infants in the EPI DR-CPR group had favorable outcomes compared with 44% in the VPI DR-CPR group. Significantly higher ORs for mortality, IVH and ROP were found in the VPI compared to the EPI group.

CONCLUSION: Preterm VLBW infants requiring DR-CPR were at increased risk of adverse outcomes compared to those not requiring CPR. This effect was more pronounced in the VPI group.

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INTRODUCTION

The impending delivery of a preterm infant is a distressing event for parents and caregivers alike. One issue commonly discussed with parents is the possible need for cardiopulmonary resuscitation (CPR) in the delivery room (DR) and its possible affect on the infant's short- and long-term prognoses. In the mid-1980s, a retrospective study of 38 very low birth weight (VLBW) infants who underwent CPR within the first 3 days of life reported that none survived,[1] concluding that VLBW infants should not automatically receive CPR. Since then, outcome studies have been more encouraging towards active DR-CPR, but reports on the association of DR-CPR with mortality and morbidity of VLBW infants' conflict.[2–6] Studies analyzing the outcomes of VLBW infants who underwent DR-CPR were influenced by the poor outcomes of extremely preterm infants (EPIs, born 24 to 27 weeks') even without CPR, and furthermore, may account for antenatal factors associated with DR-CPR such as steroid use, maternal chorioamnionitis, gestational age (GA), gender, multiple births, small for GA (SGA) and mode of delivery.[2] Cohorts that include referral centers from a regional network might be biased toward worse outcomes[3,5] and a single-center experience with a small number of infants who received DR-CPR may limit generalization of outcome results.[4]

We hypothesized that after adjusting for demographic and perinatal variables, DR-CPR is associated with increased mortality and morbidity, and that these adverse outcomes will affect EPI to a greater degree than it will for very preterm infants (VPIs, 28 to 31 weeks' gestation). Therefore, the aim of this study was to assess perinatal factors and outcomes of preterm, VLBW infants requiring DR-CPR in a large, population-based cohort of VLBW infants.

METHODS

Israel National VLBW infant database

The Israel Neonatal Network collects data on all VLBW (⩽1500 g) infants born in Israel. This study included data from 1995 through 2010, from all 28 neonatology departments in Israel (Appendix). The information collected included parental demographic information, maternal obstetrical history and antenatal care, details of delivery, infants' status at delivery, diagnoses, procedures, complications during hospitalization and status at discharge, as previously described.[7] All departments used an operating manual and standard definitions based on those of the Vermont-Oxford Trials Network.[8] A standardized form was completed for each infant, checked for logical errors, and if necessary, returned to the participating center for clarification. Birth hospital and patient identification subsequently remain confidential by consensus agreement of all participating centers. Data are collected on all infants until discharge home or death. The study was approved by the Institutional Review Board of Sheba Medical Center.

Definitions

DR-CPR was defined as administration of chest compressions with or without epinephrine in the DR. Definitions of the perinatal variables included in the analysis have been previously reported.[7] GA in completed weeks was defined as the best estimate based on last menstrual period,

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obstetric history and examination, prenatal ultrasound or early postnatal physical examination. SGA was defined as a BW $<$10th percentile for GA according to the gender-specific growth charts of Kramer *et al.*[9] Prolonged rupture of membranes (PROM) was considered as rupture of membranes longer than 24 h before delivery. The diagnosis of chorioamnionitis was established clinically based on commonly accepted criteria by the obstetricians at all study hospitals. Antenatal steroid therapy defined as 'partial', if delivery occurred within 24 h after the first dose or more than a week after the last dose, or 'complete' therapy if delivery occurred from 24 h to 7 days after completion of the course with two doses of betamethasone, 24 h apart. Respiratory distress syndrome was diagnosed by chest radiograph as consistent with respiratory distress syndrome, together with need for supplemental oxygen or mechanical ventilation therapy. Bronchopulmonary dysplasia (BPD) was diagnosed according to the criteria of Bancalari *et al.*[10] including clinical and radiologic features, together with a need for oxygen therapy at 36 weeks post menstrual age. Retinopathy of prematurity (ROP) was graded according to the international classification[11] and was recorded as the most severe stage in either eye. Intraventricular hemorrhage (IVH) was diagnosed by cranial ultrasound and graded according to Papile *et al.*[12] Periventricular leukomalacia (PVL) was diagnosed by the presence of multiple periventricular cysts identified by ultrasound after 28 days of life. Necrotizing enterocolitis (NEC) was determined by the clinical and radiological criteria of Bell *et al.*,[13] and only definite NEC (Bell stages II to III) was included. Mortality was defined as death prior to discharge home. Composite adverse outcomes were defined as mortality or one or more major morbidity, including IVH grades 3 to 4, PVL, ROP grades 3 to 4, BPD or NEC. Outcome variables were calculated only for infants who survived and reached the appropriate postnatal age (for example, BPD was calculated only for infants who reached 36 weeks post menstrual age).

Study population

The 16-year study period (1995 through 2010) included records of 24 250 VLBW infants, representing $>$99% of all VLBW infants born in Israel (Figure 1). For the purpose of this analysis, infants born before 24 weeks' gestation ($n=1134$) or after 31 weeks' gestation ($n=5360$), those who received comfort care only in the DR (no CPR, no intubation and died in the DR) ($n=112$ EPIs), and those who had lethal congenital malformations ($n=66$) or missing data ($n=14$) were excluded. The final study population comprised 17 564 VLBW infants born at 24 to 31 weeks' gestation. Extremely preterm was considered as GA 24 to 27 weeks ($n=6478$ infants) and very preterm as GA 28 to 31 weeks ($n=11\,086$ infants).

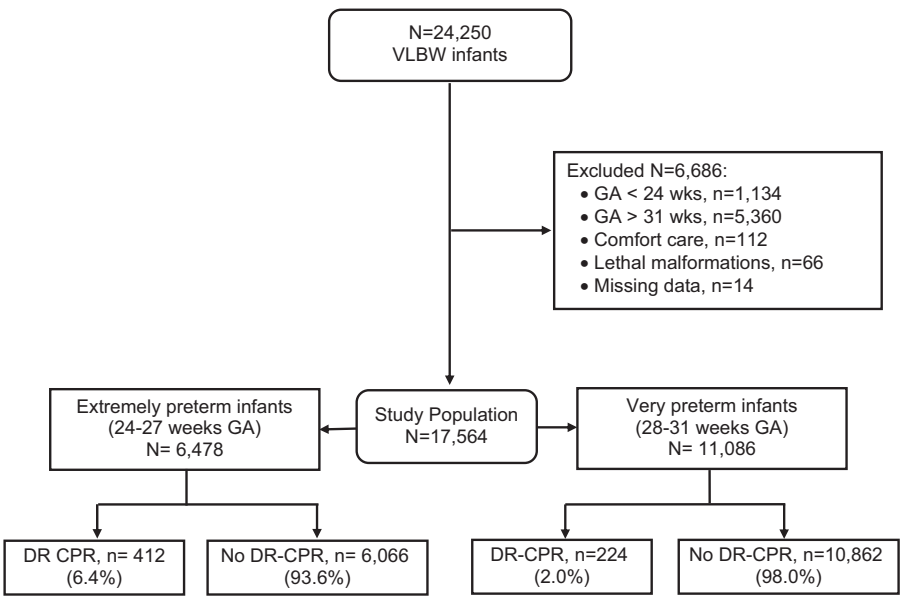
Statistical analysis

The antenatal and neonatal variables between the DR-CPR and the no DR-CPR groups were compared using the χ^2-test for categorical variables and two-sample *t*-test for continuous variables. All tests were two-sided and *P*-values <0.05 were considered significant. As *P*-values were not adjusted for multiple testing, they should be considered descriptive.

Multivariable logistic regression analyses were used to first identify the factors independently associated with DR-CPR in the EPI and VPI groups separately, and then to assess the impact of DR-CPR on neonatal outcomes in the two groups. The multivariable analyses were adjusted for maternal variables (multiple pregnancy, ethnicity, fertility treatment, initiation of prenatal care, hypertensive disorders (including chronic hypertension and pregnancy-induced hypertension), diabetes (pregestational and gestational), antenatal steroid therapy, preterm labor, antepartum hemorrhage, PROM, amnionitis and cesarean delivery) and for neonatal variables (GA, SGA, gender and non-lethal congenital malformations). In view of the strong correlation between BW and GA, BW was excluded from the multivariable analyses. Results of the multivariable analyses are presented as adjusted odds ratios (ORs) with 95% confidence intervals. To evaluate potential heterogeneity in the effect of DR-CPR in the EPI and VPI groups, we analyzed the DR $\times$ CPR group interaction term in the full multivariable models. A statistically significant interaction indicates that this effect differed between the EPI and VPI groups. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Among 17 564 VLBW infants, 636 (3.6%) received DR-CPR (Figure 1). In the group of 6478 EPI, 412 (6.4%) received DR-CPR compared with 224 of 11 086 infants (2.0%) in the VPI group. The univariate analyses of factors associated with DR-CPR in the EPI and the VPI groups are shown in Tables 1a and b, respectively. In both groups, a higher proportion of infants with younger GA, later initiation of prenatal care, singleton births, male gender and lower BW were in the DR-CPR group, whereas a higher proportion of antenatal steroid therapy was found in the no DR-CPR group. In the EPI, the rate of SGA was higher in the DR-CPR group. Among the infants in the VPI group requiring DR-CPR, the rates of antepartum hemorrhage and cesarean deliveries were significantly higher. Multivariable logistic regression analyses evaluating



VLBW, Very low birth weight; GA, Gestational age; DR-CPR, Delivery room cardiopulmonary resuscitation

Figure 1. Schematic description of the study population.

Table 1a. Demographic and perinatal characteristics of extremely preterm infants born 24–27 weeks' gestation receiving or not receiving delivery room cardiopulmonary resuscitation

	DR-CPR (N = 412)	*No DR-CPR (N = 6066)*	
Variable	N *(%)*	N *(%)*	P-*value*
Gestational age (weeks)			
24	129 (31.3)	985 (16.2)	< 0.0001
25	106 (25.7)	1274 (21.0)	
26	89 (21.6)	1712 (28.2)	
27	88 (21.4)	2095 (34.6)	
Maternal age (year) (mean ± s.d.)	29.4 ± 6.7	29.3 ± 6.1	0.71
Plurality			< 0.001
Singleton	293 (71.1)	3781 (62.3)	
Multiple	119 (28.9)	2285 (37.7)	
Infertility treatment	108 (26.7)	1888 (31.3)	0.06
Start of prenatal care (weeks)			0.0001
0–12	321 (77.9)	5046 (83.2)	
13–20	30 (7.3)	470 (7.7)	
> 20	29 (7.0)	292 (4.8)	
Unknown	32 (7.8)	258 (4.3)	
Maternal hypertension	40 (9.9)	667 (11.0)	0.48
Maternal diabetes	16 (3.9)	273 (4.5)	0.60
Antenatal steroids			< 0.0001
Complete	116 (28.6)	2865 (47.3)	
Partial	78 (19.2)	1190 (19.7)	
None	212 (52.2)	2000 (33.0)	
Preterm labor	273 (66.7)	3893 (64.2)	0.30
Antepartum hemorrhage	106 (25.9)	1366 (22.6)	0.12
PROM/amnionitis			*0.08*
No amnionitis/ROM < 24 h	303 (73.5)	4441 (73.2)	
No amnionitis/ROM ⩾ 24 h	37 (9.0)	754 (12.4)	
Amnionitis	62 (15.1)	724 (11.9)	
Unknown	10 (2.4)	147 (2.5)	
Cesarean delivery	254 (61.6)	3685 (60.7)	0.72
Male gender	274 (66.5)	3339 (55.0)	< 0.0001
Birth weight (g)			< 0.0001
< 750	204 (49.5)	2196 (36.2)	
750–999	160 (38.8)	2742 (45.2)	
1000–1249	44 (10.7)	1037 (17.1)	
1250–1500	4 (1.0)	91 (1.5)	
SGA	61 (14.8)	647 (10.7)	< 0.01
Non-lethal congenital malformation	25 (6.8)	294 (4.9)	0.10
Apgar 1 min < 4	311 (78.1)	1409 (24.0)	< 0.0001
Apgar 5 min < 4	166 (42.2)	227 (3.9)	< 0.0001

Abbreviations: Amnionitis, clinical chorioamnionitis; DR-CPR, delivery room cardiopulmonary resuscitation; PROM, prolonged rupture of membranes; SGA, small for gestational age.

Table 1b. Demographic and perinatal characteristics for very preterm infants born 28–31 weeks' gestation receiving or not receiving delivery room cardiopulmonary resuscitation

	DR-CPR (N = 224)	*No DR-CPR (N = 10 862)*	
Variable	N *(%)*	N *(%)*	P-*value*
Gestational age (weeks)			
28	82 (36.6)	2649 (24.4)	< 0.0001
29	63 (28.1)	2809 (25.9)	
30	50 (22.3)	2875 (26.5)	
31	29 (12.9)	2529 (23.3)	
Maternal age (years) (mean ± s.d.)	30.3 ± 6.7	29.7 ± 6.0	0.21
Plurality			< 0.001
Singleton	152 (67.9)	6106 (56.2)	
Multiple	72 (32.1)	4756 (43.8)	
Infertility treatment	55 (24.8)	3696 (34.1)	< 0.01
Start of prenatal care (weeks)			< 0.01
0–12	175 (78.1)	9103 (83.8)	
13–20	17 (7.6)	882 (8.1)	
> 20	19 (8.5)	523 (4.8)	
Unknown	13 (5.8)	354 (3.3)	
Maternal hypertension	46 (20.9)	2302 (21.2)	0.91
Maternal diabetes	14 (6.4)	745 (6.9)	0.78
Antenatal steroids			< 0.0001
Complete	84 (37.7)	6144 (56.7)	
Partial	105 (47.1)	1755 (16.2)	
None	34 (15.2)	2938 (27.1)	
Preterm labor	110 (49.1)	5974 (55.0)	0.08
Antepartum hemorrhage	64 (28.7)	1650 (15.2)	< 0.0001
PROM/amnionitis			0.59
No amnionitis/ROM < 24 h	180 (80.4)	8590 (79.1)	
No amnionitis/ROM ⩾ 24 h	24 (10.7)	1337 (12.3)	
Amnionitis	16 (7.1)	633 (5.8)	
Unknown	4 (1.8)	302 (2.8)	
Cesarean delivery	194 (86.6)	8081 (74.4)	< 0.0001
Male gender	138 (61.9)	5502 (50.6)	< 0.001
Birth weight (g)			< 0.001
< 750	12 (5.4)	392 (3.6)	
750–999	44 (19.6)	1633 (15.0)	
1000–1249	96 (42.9)	3958 (36.5)	
1250–1500	72 (32.1)	4879 (44.9)	
SGA	52 (23.2)	1996 (18.4)	0.06
Non-lethal congenital malformation	24 (11.1)	803 (7.4)	0.04
Apgar 1 min < 4	161 (73.2)	967 (9.0)	< 0.0001
Apgar 5 min < 4	77 (36.3)	67 (0.6)	< 0.0001

Abbreviations: Amnionitis, clinical chorioamnionitis; DR-CPR, delivery room cardiopulmonary resuscitation; PROM, prolonged rupture of membranes; SGA, small for gestational age.

factors independently associated with DR-CPR in both groups are shown in Table 2. The ORs for DR-CPR were significantly higher with lower GA, singleton birth, no antenatal steroids, cesarean delivery and male gender. DR-CPR was significantly associated with chorioamnionitis and SGA in the EPI group, and antepartum hemorrhage was significant in VPI group.

The outcomes after DR-CPR compared to no DR-CPR in the EPI and VPI groups are shown in Table 3. In both groups, rates of mortality, respiratory distress syndrome, IVH grades 3 to 4 and BPD were higher in infants receiving DR-CPR. Among infants receiving DR-CPR, the rates of early and late sepsis and ROP grades 3 to 4 were significantly higher in the VPI group only, and

Table 2. Percent delivery room cardiopulmonary resuscitation and multivariable logistic regression analyses of factors independently associated with DR-CPR among extremely preterm (24–27 weeks' gestation) and very preterm (28–31 weeks' gestation) infants

	Percent DR-CPR		*DR-CPR OR (95% CI)*[a]	
Variable	*24–27 weeks*	*28–31 weeks*	*24–27 weeks*	*28–31 weeks*
Gestational age (weeks)				
24 28	11.6	3.0	**2.65 (1.95, 3.60)**	**2.69 (1.75, 4.19)**
25 29	7.7	2.2	**1.75 (1.30, 2.38)**	**1.91 (1.21, 3.02)**
26 30	4.9	1.7	1.18 (0.87, 1.60)	1.54 (0.96, 2.46)
27 31	4.0	1.1	1.0	1.0
Maternal age (years) each 10-year increase			1.01 (0.84, 1.20)	1.18 (0.93, 2.15)
Multiple birth	4.9	1.5	1.0	1.0
Singleton	7.2	2.4	**1.69 (1.27, 2.27)**	**1.43 (1.00, 2.04)**
Infertility treatment				
No	6.7	2.3	1.0	1.0
Yes	5.4	1.5	1.16 (0.86, 1.57)	0.96 (0.65, 1.40)
Start prenatal care (weeks)				
0–12	6.0	1.9	1.0	1.0
13–20	6.0	1.9	0.97 (0.65, 1.47)	0.82 (0.48, 1.40)
>20	9.0	3.5	1.26 (0.82, 1.94)	1.41 (0.84, 2.37)
Unknown	11.0	3.5	1.41 (0.92, 2.16)	1.57 (0.85, 2.89)
Maternal hypertension				
No	6.3	2.0	1.0	1.0
Yes	5.7	2.0	0.90 (0.60, 1.35)	0.89 (0.61, 1.31)
Maternal diabetes				
No	6.3	2.0	1.0	1.0
Yes	5.5	1.8	1.01 (0.59, 1.75)	1.00 (0.57, 1.77)
Antenatal steroids				
Complete	3.9	1.3	1.0	1.0
Partial	6.1	1.9	**1.61 (1.18, 2.19)**	1.42 (0.93, 2.15)
None	9.6	3.4	**2.45 (1.90, 3.16)**	**2.46 (1.80, 3.36)**
Preterm labor				
No	5.9	2.3	1.0	1.0
Yes	6.5	1.8	1.20 (0.94, 1.53)	1.11 (0.82, 1.52)
Antepartum hemorrhage				
No	6.1	1.7	1.0	1.0
Yes	7.2	3.7	1.04 (0.81, 1.34)	**1.72 (1.25, 2.37)**
PROM/amnionitis				
No amnio/PROM < 24 h	6.4	2.0	1.0	1.0
No amnio/PROM ⩾ 24 h	4.7	1.8	0.94 (0.64, 1.38)	1.18 (0.75, 1.86)
Amnionitis	7.9	2.5	**1.39 (1.02, 1.91)**	1.34 (0.78, 2.32)
Unknown	6.4	1.3	1.07 (0.53, 2.16)	0.55 (0.17, 1.75)
Vaginal delivery	6.2	1.1	1.0	1.0
Cesarean section	6.4	2.3	**1.63 (1.28, 2.06)**	**2.51 (1.65, 3.82)**
Female	4.8	1.6	1.0	1.0
Male	7.6	2.4	**1.64 (1.30, 2.04)**	**1.47 (1.12, 1.96)**
SGA				
No	6.1	1.9	1.0	1.0
Yes	8.6	2.5	**1.42 (1.02, 1.98)**	1.40 (0.98, 2.00)
Congenital malformation				
No	5.6	1.9	1.0	1.0
Yes	7.8	2.9	1.51 (0.98, 2.32)	1.39 (0.90, 2.16)

Abbreviations: Amnionitis, clinical chorioamnionitis; CI, confidence interval; DR-CPR, delivery room cardiopulmonary resuscitation; OR, odds ratio; PROM, prolonged rupture of membranes; SGA, small for gestational age. [a]Odds ratio (95% confidence interval) in multivariable models adjusted for gestational age, maternal age, infertility treatment, start of prenatal care, maternal hypertension, maternal diabetes, preterm labor, antepartum hemorrhage, prolonged rupture of membranes/amnionitis, multiple birth, antenatal steroids, mode of delivery, gender, small for gestational age and non-lethal congenital malformations (significant results highlighted in bold font).

Table 3. Neonatal outcomes of extremely preterm (24–27 weeks' gestation) and very preterm (28–31 weeks' gestation) infants after delivery room cardiopulmonary resuscitation compared to no DR-CPR

	Extremely preterm infants (24–27 weeks)					*Very preterm infants (28–31 weeks)*				
	DR-CPR		*No DR-CPR*			*DR-CPR*		*No DR-CPR*		
Outcome	N[a]	*%*	N[a]	*%*	P-*value*	N[a]	*%*	N[a]	*%*	P-*value*
Mortality	412	70.9	6066	34.8	< **0.0001**	224	32.6	10 862	6.1	< **0.001**
Early sepsis	367	4.9	6035	3.9	0.36	213	4.7	10 856	2.0	< **0.01**
Late sepsis	213	52.1	5179	50.9	0.74	176	33.5	10 663	24.8	< **0.01**
RDS	368	95.6	6039	91.1	< **0.01**	213	80.7	10 858	63.9	< **0.0001**
IVH grades 3 and 4	250	39.6	5480	25.2	< **0.0001**	183	21.9	10 390	5.4	< **0.0001**
PVL	138	20.3	4083	11.2	**0.001**	144	9.0	8839	5.3	0.05
ROP grades 3 and 4	140	22.9	4162	19.0	0.25	153	5.2	9777	1.8	< **0.01**
NEC	368	6.8	6039	10.1	**0.04**	213	6.6	10 855	5.1	0.33
BPD	126	42.1	3924	31.7	**0.01**	148	12.8	10 192	7.5	< **0.01**
Composite outcomes										
Death/IVH 3 and 4, PVL, ROP 3 and 4	412	83.0	6066	56.7	< **0.0001**	224	47.3	10 862	14.2	< **0.0001**
Death/BPD	412	81.3	6066	53.5	< **0.0001**	224	39.7	10 862	12.6	< **0.0001**
Death/IVH 3 and 4/PVL/ROP 3 and 4/BPD/NEC	412	89.1	6066	68.9	< **0.0001**	224	55.8	10 862	22.6	< **0.0001**

Abbreviations: BPD, bronchopulmonary dysplasia; DR-CPR, delivery room cardiopulmonary resuscitation; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity. [a]Number of infants examined for each outcome (significant results highlighted in bold).

Table 4. Multivariable logistic regression analysis for mortality and neonatal outcomes in infants receiving delivery room cardiopulmonary resuscitation compared with no DR-CPR in the extremely preterm and very preterm infant groups

	Extremely preterm infants (24–27 weeks' gestation)	*Very preterm infants (28–31 weeks' gestation)*	
	DR-CPR vs no DR-CPR	*DR-CPR vs no DR-CPR*	
Outcome	*OR (95% CI)*[a]	*OR (95% CI)*[a]	P *for Interaction*
Mortality	3.32 (2.58, 4.29)	4.99 (3.59, 6.94)	0.01
Early sepsis	1.10 (0.65, 1.86)	2.07 (1.05, 4.09)	0.09
Late sepsis	0.98 (0.74, 1.29)	1.30 (0.94, 1.80)	0.07
RDS	1.67 (0.99, 2.81)	1.83 (1.27, 2.62)	0.66
IVH grades 3 and 4	1.59 (1.20, 2.10)	3.74 (2.55, 5.50)	< 0.0001
PVL	1.81 (1.17, 2.82)	1.39 (0.77, 2.52)	0.71
ROP grades 3 and 4	0.97 (0.63, 1.50)	2.53 (1.18, 5.41)	0.03
NEC	0.61 (0.40, 0.92)	1.09 (0.63, 1.91)	0.06
BPD	1.32 (0.90, 1.94)	1.42 (0.85, 2.36)	0.66
Composite outcomes			
Death/IVH 3 and 4, PVL, ROP 3 and 4	2.49 (1.86, 3.33)	3.83 (2.85, 5.15)	0.03
Death/BPD	2.62 (1.98, 3.47)	3.14 (2.31, 4.28)	0.30
Death/IVH 3 and 4/PVL, ROP 3 and 4/ BPD/NEC	2.41 (1.72, 3.37)	3.11 (2.33, 4.16)	0.29

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; DR-CPR, delivery room cardiopulmonary resuscitation; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; OR, odds ratio; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity. [a]Odds ratio (95% confidence interval) in multivariable models adjusted for gestational age, maternal age, infertility treatment, start of prenatal care, maternal hypertension, maternal diabetes, preterm labor, antepartum hemorrhage, prolonged rupture of membranes/amnionitis, multiple birth, antenatal steroids, mode of delivery, gender, small for gestational age and non-lethal congenital malformations.

the rate of PVL was higher in the EPI group. The rates of composite adverse outcomes of death or neonatal morbidities were significantly higher among infants receiving DR-CPR in both groups.

After adjusting for confounding variables, DR-CPR was a significant predictor of mortality, IVH grades 3 to 4 and composite adverse outcomes in both groups of infants (Table 4). In the VPI group, DR-CPR was a significant predictor of early sepsis, respiratory distress syndrome and ROP grades 3 to 4. The EPI who received DR-CPR had a significantly higher OR for PVL and lower OR for NEC compared to infants not requiring CPR. The effect of DR-CPR on mortality was more pronounced in the VPI group compared to the EPI group (OR 4.99, 95% confidence interval 3.59 to 6.94 and OR 3.32, 95% confidence interval 2.58 to 4.29, respectively; *P* for interaction = 0.01). Similarly, significantly higher ORs were found in the VPI group compared to the EPI

group requiring DR-CPR, for IVH grades 3 to 4 (P for interaction < 0.0001), for ROP grades 3 to 4 (P for interaction $= 0.03$), and for the composite outcome of death or IVH, PVL or ROP (P for interaction $= 0.03$).

Comments

This study confirms that DR-CPR was a significant predictor of death or adverse outcomes in both extremely preterm (24 to 27 weeks GA) and very preterm (28 to 31 weeks GA), VLBW infants. These findings are in agreement with our hypothesis that the need for DR-CPR was associated with adverse neonatal outcomes. However, we also determined that in the more mature group of VPIs requiring DR-CPR, the ORs of adverse outcomes of mortality, IVH and ROP were significantly higher compared to the EPIs requiring DR-CPR.

The lower ORs for adverse outcomes in the EPI group requiring DR-CPR might reflect the high rates of mortality and morbidities among the EPI group both with and without DR-CPR. The effect of DR-CPR on adverse outcomes is thus less pronounced in the EPI group compared to VPI group, where outcomes in infants not requiring DR-CPR were markedly better. Another explanation could be that DR-CPR might have been more intense and prolonged among the more mature preterm infants, when clinicians believed it was more likely to be successful.[14]

The findings of this study agree with those of two recent reports demonstrating that although more mature infants are less likely to receive DR-CPR, the degree of increased adverse outcomes is higher.[5,6] Handley *et al*.[6] found that infants 26 to $27^{6/7}$ weeks' receiving DR-CPR were more likely to die and have severe IVH compared to those who did not. This outcome difference was not recorded in the group born at 24 to $25^{6/7}$ weeks' gestation, where adverse outcomes were common regardless of DR-CPR. Soraisham *et al*.[5] found that infants born before 33 weeks' gestation who underwent DR-CPR had increased risk of mortality and morbidity, especially those weighing >1000 g compared to 1000 g or less.

While most studies show increased mortality and morbidity after DR-CPR across all GA groups, reports of the relationship between DR-CPR and specific morbidities are inconsistent, which might be due to different study populations and treatment policies. The increased risk for grades 3 to 4 IVH and PVL in infants undergoing DR-CPR in our study is not surprising, given that fluctuations in blood pressure are associated with IVH and PVL.[15,16] Infants receiving CPR might experience very low blood pressure during asphyxia-induced bradycardia and rebound hypertension following epinephrine administration. Furthermore, during DR-CPR, fluctuations in blood pressure can also result from variations in cardiac compression, degree of positive pressure ventilation applied and oxygen levels used. In the current study, information on the quality of, or variations in the delivery techniques of cardiac compressions or inflation pressures and FiO_2 used by the individual departments was not available. Therefore, these data cannot be correlated to outcomes. Increased rates of BPD after DR-CPR might be related to barotrauma from aggressive positive pressure ventilation and to significant oxygen exposure during the resuscitation.[17]

Prenatal factors independently associated with the need for DR-CPR in this study were lower GA, singleton birth, no maternal prenatal steroid treatment, cesarean delivery and male gender in both groups, and in addition, amnionitis and SGA in the EPI group, and antepartum hemorrhage in the VPI group. This agrees with the study by Wyckoff *et al*.[2] that showed that antepartum hemorrhage, younger GA, lower BW and male gender were associated with increased likelihood of receiving DR-CPR. They also demonstrated that vaginal breech delivery was associated with increased likelihood of CPR. However, our results showed a 1.6- to 2.5-fold higher OR for DR-CPR among infants delivered by cesarean section. The database does not include the indication for cesarean delivery. However, since more of the VLBW infants who underwent DR-CPR in our study had amnionitis (EPI group) and antenatal hemorrhage (VPI group), we speculate that this may reflect the performance of emergent cesarean deliveries in patients with evidence of acute fetal distress and perinatal complications, and hence, the necessity for subsequent DR-CPR.

Due to high mortality and poor outcomes after DR-CPR, the question remains whether it should be considered futile therapy, especially for EPI, as was noted by Lantos *et al*.[1] The VON study[3] showed that for infants weighing <1000 g, survival was 53.8% with DR-CPR compared to 74.9% without. In addition, severe IVH occurred in 15.3% of infants who received DR-CPR compared with 4.9% of the infants who did not. Data on other outcomes were not presented.[3] They concluded that because more than half survived and that half of the survivors were free of IVH, CPR was a reasonable intervention for VLBW infants. The National Institute of child health and Human Development study on VLBW infants born from 1996 through 2002 showed survival and intact neurodevelopment in only 28% of CPR survivors at 18 to 22 months of age.[2] Therefore, the authors stressed that the significant mortality and morbidity in VLBW infants undergoing CPR suggests that the techniques should be improved. In our study, 29% of the EPI group survived after DR-CPR, but only 11% had favorable outcomes, and among the VPI group, 67.4% survived after DR-CPR, with 44.2% favorable outcomes (survival to discharge without IVH grades 3 to 4, PVL, ROP grades 3 to 4, BPD or NEC). The results among our cohort emphasize that DR-CPR in both extremely preterm and very preterm VLBW infants was still a significant predictor of adverse outcomes.

This national, population-based study included over 99% of all VLBW infants born in Israel. Almost all neonates were treated at their birth hospitals and all were followed until death or discharge home. The population-based study design enabled evaluation of multiple outcomes and is useful when exposure is relatively infrequent. More importantly, this design removed bias in determining exposure to DR-CPR, because the data were collected prospectively. The results of this study can be used as reference data for future studies evaluating the success of new DR-CPR techniques on reducing adverse outcomes.

The limitations of the study include its observational nature, the lack of standardization for the indications for CPR and its technical performance including cognitive application of the resuscitation algorithm, behavior of the team or all of the above. Furthermore, the possibility of inaccuracies in GA estimation should be considered. Since all of our population benefits from the National Health Care system for antenatal care and $>80\%$ of the pregnant women in the Jewish population and 60% in the Arab population undergo a sonogram in the first trimester, we consider these data reliable.[18] Variations in neonatal care beyond the DR may also have affected outcomes. However as noted, birth hospitals were not identified, and differences in management and outcomes in the various perinatal centers could not be assessed. Furthermore, over the 16-year study period, it is likely that there were some important changes in DR-CPR techniques, which were not included in our analysis due to lack of information about actual implementation of these variations at each site. We also could not determine whether composite adverse outcomes noted after DR-CPR are a marker of greater severity of illness at birth, an adverse effect of intensive resuscitation or a combination of both. Finally, the database does not include information regarding long-term neurodevelopment outcomes, which would enable evaluating the impact of DR-CPR among the surviving infants.

In conclusion, this study evaluated risk factors and neonatal outcomes associated with DR-CPR among infants born at 24 to 31 weeks' gestation, using 16 years of data from a national registry. We found that DR-CPR was a significant predictor of adverse composite outcomes, especially in the more mature group of preterm infants where DR-CPR was performed less often.

We conclude that DR-CPR is a marker for composite adverse outcomes among VLBW preterm infants. Addressing modifiable prenatal factors associated with DR-CPR might decrease its incidence and potentially improve neonatal outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

The Israel Neonatal Network, participating centers in the Israel National Very Low Birth Weight Infant database

Coordinating center

The Women and Children's Health Research Unit, Gertner Institute, Tel Hashomer.

Neonatology departments

Assaf Harofeh Medical Center, Rishon Le Zion; Barzilay Medical Center, Ashkelon; Bikur Holim Hospital, Jerusalem; Bnei Zion Medical Center, Haifa; Carmel Medical Center, Haifa; English (Scottish) Hospital, Nazareth; French Hospital, Nazareth; Hadassah University Hospital Ein Kerem, Jerusalem; Hadassah University Hospital Har Hazofim, Jerusalem; Haemek Medical Center, Afula; Hillel Yafe Medical Center, Hadera; Italian Hospital, Nazareth; Kaplan Hospital, Rehovot; Laniado Hospital, Netanya; Maayanei Hayeshua Hospital, Bnei Brak; Meir Medical Center, Kfar Saba; Misgav Ladach Hospital, Jerusalem; Naharia Hospital, Naharia; Poria Hospital, Tiberias; Rambam Medical Center, Haifa; Rivka Ziv Hospital, Safed; Schneider Children's Medical Center of Israel, Petach Tikva; Rabin Medical Center (Beilinson Campus), Petach Tikva; Shaare Zedek Hospital, Jerusalem; Sheba Medical Center, Tel Hashomer; Soroka Medical Center, Beer Sheba; Sourasky Medical Center, Tel Aviv; Wolfson Medical Center, Holon; Yoseftal Hospital, Eilat.