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Improved survival and neurodevelopmental outcomes among extremely premature infants born near the limit of viability

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ABSTRACT

Background: Infants born near the limit of viability are at high risk for death or adverse neurodevelopmental outcomes. It is unclear whether these outcomes have improved over the past 15 years.
Aim: To determine if death and neurodevelopmental impairment have declined over the past 15 years in infants born at 22 to 24 weeks' gestation.
Study design: Retrospective cohort study.
Subjects: We identified infants born at 22 to 24 weeks' gestation in our center in two epochs: 1998–2004 (Epoch 1) and 2005–2011 (Epoch 2).
Outcome measures: The primary outcome, death or neurodevelopmental impairment, was evaluated at 17–25 months' corrected gestational age with neurologic exams and Bayley Scales of Infant Development. Perinatal characteristics, major morbidities, and outcomes were compared between epochs.
Results: Birth weight and gestational age were similar between 170 infants in Epoch 1 and 187 infants in Epoch 2. Mortality was significantly lower in Epoch 2, 55% vs. 42% ($p = 0.02$). Among surviving infants, late-onset sepsis ($p < 0.01$), bronchopulmonary dysplasia ($p < 0.01$), and surgical necrotizing enterocolitis ($p = 0.04$) were less common in Epoch 2. Neurodevelopmental impairment among surviving infants declined from 68% in Epoch 1 to 47% in Epoch 2, $p = 0.02$. Odds of death or NDI were significantly lower in Epoch 2 vs. Epoch 1, OR = 0.31 (95% confidence interval; 0.16, 0.58).
Conclusion: Risk of death or neurodevelopmental impairment decreased over time in infants born at 22 to 24 weeks' gestation.

1. Introduction

Infants born near the limit of viability are at high risk for death or adverse neurodevelopmental outcomes [1–5]. Recent evidence suggests that survival has improved in this population over the past 20 years [5,6], but there is little evidence that neurodevelopmental outcomes of surviving infants have changed. Two multicenter studies by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network reported that neurodevelopmental outcomes did not improve the over consecutive birth epochs in infants born 22–24 weeks' gestation between 1993 and 2004 [1,4]. The most recent of these studies reported death in 67.6% of these infants in 2002–2004, and neurodevelopmental impairment (NDI) in 58.7% of survivors [4]. A recent study from Japan's Neonatal Research Network described better than previously reported outcomes in this group, with death or NDI seen in 80.0% of infants born at 22 weeks' gestation, 63.7% at 23 weeks' gestation, and 38.9% at 24 weeks' gestation [7]. Current knowledge of outcomes for infants born at these early gestational ages is critical for clinicians and families when making early obstetrical and neonatal care decisions [8].

The objective of this study was to compare death and early childhood neurodevelopmental outcomes for infants born <25 weeks' gestation in our center between two recent birth epochs.

2. Methods

2.1. Study population

We identified all infants born 22 0/7–24 6/7 weeks' gestation that were admitted to the Neonatal Intensive Care Unit at Duke University Medical Center from January 1, 1998 to December 31, 2011. Infants admitted from an outside hospital at >48 h of age were excluded. The study period was divided into two epochs. Epoch 1 included infants

Abbreviations: BPD, Bronchopulmonary dysplasia; CP, Cerebral palsy; GA, Gestational age; IVH, Intraventricular hemorrhage; NEC, Necrotizing enterocolitis; NDI, Neurodevelopmental impairment; PDA, Patent ductus arteriosus; ROP, Retinopathy of prematurity.

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born from 1998 to 2004 and Epoch 2 included infants born from 2005 to 2011. Epoch 1 was chosen to overlap with the most recent NICHD Neonatal Research Network study showing no improvement in neurodevelopmental outcomes over time in this population, and Epoch 2 includes the years since this study [4]. Our study was approved by the Duke Institutional Review Board.

2.2. Measures

Inpatient charts were reviewed to determine perinatal characteristics and neonatal morbidities. Antenatal steroid use was defined as any steroid exposure in the current pregnancy to accelerate fetal lung maturity. Severe intraventricular hemorrhage (IVH) was defined as unilateral or bilateral grade 3 or 4 hemorrhage [9]. Severe retinopathy of prematurity (ROP) was defined as stage 3 or 4 disease requiring laser therapy. Sepsis was defined as ≥1 positive blood culture requiring antibiotic treatment. Sepsis was classified as early-onset if occurring in the first 3 days of life or late-onset sepsis if occurring after 72 postnatal hours. Necrotizing enterocolitis (NEC) was defined by modified Bell's staging criteria, stage IIA or greater [10]. Bronchopulmonary dysplasia (BPD) was defined as the need for supplemental oxygen at 36 weeks' postmenstrual age. Receipt of postnatal dexamethasone for prevention or treatment of BPD was also noted.

After discharge, the infants were followed in the Duke Special Infant Care Clinic. Neurodevelopmental outcomes were assessed at 17–25 months' corrected gestational age (GA) with neurologic examinations performed by a physician trained in neurodevelopmental assessments and Bayley Scales of Infant Development performed by a licensed clinical psychologist. The Bayley II was used from 1998 to 2007 and the Bayley III was used from 2008 to 2011 [11,12]. Data for infants who received follow-up care at outside clinics or outside of the 17–25 months' corrected GA window were not included in the analysis. Death included in-hospital deaths as well as deaths that occurred from the time of discharge to the follow-up period. Neurodevelopmental impairment (NDI) was defined as any of the following: moderate or severe cerebral palsy (CP), significant cognitive impairment [mental developmental index < 70 (Bayley II) or cognitive composite score < 85 (Bayley III)], significant motor impairment [psychomotor developmental index < 70 (Bayley II) or motor composite score < 70 (Bayley III)], or bilateral blindness. We used the higher cognitive composite cut-off score of <85 on the Bayley III for comparison with the Bayley II mental developmental index of <70 to improve consistency based on previous studies showing that the Bayley III overestimates cognitive performance relative to the Bayley II [13–16]. CP was defined as a static neurologic disorder characterized by abnormal muscle tone affecting at least one extremity and interfering with motor function. Those with moderate or severe CP required assistive device(s) for ambulation or were non-ambulatory at the time of follow-up.

2.3. Statistical methods

Our primary outcome was death or NDI, as defined above. Secondary outcomes included death alone and each component of NDI alone in surviving infants who were seen in follow-up. Outcomes, including in-hospital outcomes such as severe IVH and severe ROP, were compared between groups using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous data. We also compared outcomes across epochs for subgroups of infants born at 23 weeks and 24 weeks of gestation. We did not include the 22 week infants as a separate subgroup given the low number of survivors at this gestational age. Risk of death or NDI by epoch was compared using logistic regression to control for GA at birth.

For all tests, significance was defined as $p < 0.05$. Statistical analysis was performed using Stata version 12 (College Station, TX, USA).

3. Results

During the study period, a total of 357 infants were born at 22–24 weeks of gestation. Of these infants, 170 (48%) were born in Epoch 1 and 187 (52%) were born in Epoch 2. Epoch 1 and 2 infants did not differ significantly in birth weight, GA, inborn status, gender, multiple gestations, or receipt of antenatal steroids (Table 1). The proportion of infants born by cesarean delivery was higher in Epoch 2. Among surviving infants, incidence of severe IVH, periventricular leukomalacia, post-hemorrhagic hydrocephalus requiring ventricular shunt, severe ROP, medical NEC, early-onset sepsis, and PDA requiring surgical ligation was similar between epochs. Incidence of BPD and use of postnatal dexamethasone were significantly lower in Epoch 2. Surgical NEC and late-onset sepsis were also less common among infants born in Epoch 2.

Data on the primary outcome was available for 140/170 (82%) of the infants in Epoch 1 and 166/187 (89%) of the infants in Epoch 2, $p = 0.10$. Post-discharge follow-up among surviving infants was 75% across the entire study period. Follow-up was significantly higher in Epoch 2, with 49 infants (64% of survivors) in Epoch 1 and 91 infants (83% of survivors) in Epoch 2 having follow-up at 17–25 months of corrected GA, $p < 0.01$. Infants with and without follow-up had similar median (range) birth weight [647.5 (410–916) g versus 640 (450–900) g, $p = 0.60$] and birth GA [24 (22–24) versus 24 (22–24) weeks, $p = 0.15$]. The proportion of infants with severe IVH was greater among infants with follow-up than those lost to follow-up [35/140 (25%) versus 3/46 (7%), $p < 0.01$]. Incidence of other major morbidities was similar between infants with and without follow-up, including periventricular leukomalacia, post-hemorrhagic hydrocephalus requiring ventricular shunt, severe ROP, PDA ligation, NEC, sepsis, and BPD (data not shown). Of the infants with follow-up data, the corrected GA at the time of follow-up was higher in Epoch 1, with a median (range) of 20 (17–25) months in Epoch 1 versus 19 (17–25) months in Epoch 2, $p = 0.03$.

Overall, death occurred in 171 of 357 infants (48%). Mortality was significantly lower in Epoch 2 compared to Epoch 1 (Table 2). The primary outcome, the composite of death or NDI, was also lower in

Table 1
Perinatal characteristics and in-hospital morbidities.

	Epoch 1 ($n = 170$)	Epoch 2 ($n = 187$)	p
Baseline characteristics			
Birth weight (g), median (range)	600 (350–916)	620 (330–904)	0.05
Birth gestational age, %			0.69
22 weeks	3	2	
23 weeks	36	35	
24 weeks	61	63	
Inborn, %	88	82	0.14
Male, %	55	55	>0.99
Multiple birth, %	28	27	0.91
Cesarean delivery, %	38	49	0.04
Antenatal steroid use, %	83	84	0.87
In-hospital morbidities and treatments[a]			
Severe IVH, %	18	22	0.58
PVL, %	9	9	>0.99
Shunt for hydrocephalus, %	5	2	0.23
Severe ROP, %	36	35	0.88
Medical NEC, %	17	9	0.17
Surgical NEC, %	16	6	0.04
Early-onset sepsis, %	1	4	0.41
Late-onset sepsis, %	75	55	<0.01
PDA ligation, %	34	39	0.54
Postnatal dexamethasone, %	55	17	<0.01
BPD, %	79	39	<0.01

IVH, Intraventricular hemorrhage; PVL, Periventricular leukomalacia; ROP, Retinopathy of prematurity; NEC, Necrotizing enterocolitis; PDA, Patent ductus arteriosus; BPD, Bronchopulmonary dysplasia.
[a] Percentages calculated from the number of infants who survived.