Underlying Causes of Death in Extreme Preterm Infants

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Abstract: Objectives: To evaluate the causes of death among extremely premature infants and to assess temporal changes in overall mortality. **Materials and methods:** We retrospectively analyzed the causes of death in all extremely premature infants with gestational ages between 23+0/7 and 28+6/7 weeks admitted to the neonatal intensive care unit at the Children's Hospital of King Fahad Medical City. We compared infants born between 2010 and 2012 to those born between 2013 and 2015. We obtained data regarding age, sex, gestational age (GA), weight at birth, infant and maternal characteristics, and cause of death. **Results:** The overall mortality rate was decreased by 14.6% from 432 (CI: 345 to 519) to 369 (CI: 286 to 452) deaths per 1,000 live births during the second period. Deaths due to prematurity and intraventricular hemorrhage were increased by 54.9% and 8.3%, respectively. Sepsis reduced by 40%, respiratory distress syndrome reduced by 42.3%, and pulmonary hemorrhage was reduced by 17%. In infants born at 23-24 weeks, prematurity caused 54% of total deaths, followed by IVH and sepsis (12.1% each). Sepsis accounted for 35.3% of deaths in infants born at 25-26 weeks. Other causes of death at this age included RDS, pulmonary hemorrhage, and prematurity (13.7% each). In infants born at 27-28 weeks of gestation, sepsis caused 20% of deaths, and RDS caused 15.5%. **Conclusion:** The overall rates of death and deaths attributed to sepsis, RDS, and pulmonary hemorrhage were reduced during the second period. Meanwhile, deaths due to prematurity and IVH have increased. Necrotizing enterocolitis, bronchopulmonary dysplasia, and congenital anomalies showed no significant trends. Causes of death were more clearly identified in the infant charts from the second period. More multicenter, prospective studies are required to implement strategies against the lethal complications of premature birth.

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Key Words: Cause-specific death rate, age-specific death rate, prematurity, sepsis, RDS (respiratory distress syndrome), BPD (bronchopulmonary dysplasia), IVH (intraventricular hemorrhage), NEC (necrotizing enterocolitis), GA (gestational age), NICU (Neonatal intensive care unit)

1. Introduction

Worldwide, the most important single cause of neonatal death is preterm birth. The World Health Organization estimates that birth weight below 2,500 g indirectly contributes to about 15% of neonatal mortality, which ranges from 6% in high-income countries to 30% in low-income countries, with preterm birth and its related complications being the underlying cause (Mmbaga, 2012).

Survival among premature infants has improved substantially over the last few decades. However, prematurity is still a leading contributor to newborn deaths worldwide (Patel, 2015). Approximately one in four extremely premature infants born at 22 to 28 weeks of gestation does not survive the ensuing hospitalization. Mortality rates decrease with each additional week of gestation (Stoll, 2010).

Changes in neonatal care, including changes in infection control, intraventricular hemorrhage (IVH) prophylaxis, and ventilation strategies, may have led to a relative decrease in the number of deaths. However, few studies on extremely premature infants have been conducted to confirm that this is indeed the case (Hintz, 2005). Few studies have reported mortality rates in gestational age-specific categories. This limits the information available to counsel parents before preterm delivery and to help with planning of the proper time and mode of delivery of an infant who will be born preterm (Butler AS, 2007). The purpose of this study was to evaluate the effects of advances in perinatal and neonatal care by investigating trends in mortality in extremely preterm infants (Gould, 2000).

2. Materials and Methods

Setting

The primary study unit was the neonatal intensive care unit (NICU) at King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia. Since the KFMC is a tertiary referral hospital, its NICU receives high-risk babies delivered within the institution and referrals from other health facilities. The NICU has a bed capacity for 44 babies. Nine of these beds are in isolation rooms, babies are nursed in incubators. The unit has sophisticated mechanical ventilators, including high frequency oscillation ventilators and inhaled nitric oxide. In addition, only registrars and fellow doctors who are Neonatal Resuscitation Program-certified are called to the labor ward to attend the extreme preterm deliveries.

Data collection and study population

Live born infants enrolled in the electronic database registry of King Fahad Medical City were included in the study if they met the following three criteria: birth between January 1, 2010 and December 31, 2016; gestational age at birth of 23+0/7 weeks to 28+6/7 weeks, and birth at KFMC or transfer to KFMC after birth in another center.

The exclusion criteria were gestational age at birth before 23 weeks, at 29 weeks, or older and babies born at KFMC but died at another center.

Upon admission, informed consent was obtained from a parent or guardian. The protocol for this study was approved by the KFMC research review board, and institutional review board approval was obtained. Data were collected by trained doctors for all live born infants. These data included gestational age, sex, weight at birth, parity, mode of delivery, singleton vs. multiple gestation, antenatal steroid and surfactant administration, and do not resuscitate (DNR) status.

Gestational age was assessed based on the date of the last menstrual period, prenatal ultrasonography, or both. If unavailable or uncertain, gestational age was determined based on the neonatologist's estimate using the physical examination criteria of Ballard (Ballard, 1979), The collection of information for neonates admitted to the NICU was performed during admission, carried on during the NICU stay, and finalized after discharge or death. The primary cause of death was identified and defined as the proximate disease or condition that led to the death. Definition of the causes of death was as following, Sepsis: Septicemia or localized infection with positive blood or organ cultures, NEC: Stage IIA or higher by Bell's criteria, IVH: Severe intracranial hemorrhage (grade III-IV) with a clinical presentation (e.g. convulsions, apnea), BPD: Infants with chronic lung disease requiring oxygen for more than 28 days with progressive respiratory insufficiency, with or without corpulmonale. Pulmonary hemorrhage: Acute onset of severe endotracheal bleeding with an acute drop in hematocrit and the development of new infiltrates on chest radiograph. Prematurity: Infants who die in the absence of infection, RDS, or massive intracranial or pulmonary bleed, or infants offered only comfort care. In situations where the cause of death was not clear, the cause of death was selected after reviewing the medical charts. Causes of death that could not be classified as one of the causes listed in the study was classified as "other". Causes of death that could not be identified after a thorough investigation was classified as "unknown".

Table 1: Characteristics of the study sample

Characteristics	**2010-2012**	**2013-2015**	**P value**
No. of live births	220	206	
No. of deaths (23-28 weeks)	95	76	
Overall mortality rare/1,000 live births (CI)	432 (345-519)	369 (286-452)	0.3059
Mean gestational age	25.5 ± 0.569	24.4 ± 0.851	0.0352*
Mean birth weight in grams	776.5 ± 0.321	690.9±0.623	<0.001*
Sex			
Male (%)	53 (55.79)	38 (50.0)	0.451
Female (%)	42 (44.21)	38 (50.0)	
Received steroids, no. (%)	91 (95.0)	71 (91)	0.51302
Received surfactants, no. (%)	72 (74.0)	69 (90.30)	0.0104*
Primigravida (%)	30 (31.58)	27 (35.53)	0.5863
Multigravida (%)	65 (68.42)	49 (64.47)	
Cesarean section (%)	54 (56.84)	31 (40.79)	0.037*
NSVD (%)	41 (43.16)	45 (59.21)	
Singleton	59 (62.11)	41 (53.95)	0.2820
Multiple gestation	36 (37.89)	35 (46.05)	
Antenatal care	69 (72.63)	56 (73.68)	0.8774
No antenatal care	26 (27.37)	20 (26.32)	

*P < 0.05; CI = confidence interval, NSVD = normal spontaneous vaginal delivery, No. = number

Statistical Analysis

Statistical data were entered into Microsoft Excel and analyzed using SPSS software, version 19.0 (IBM Corp.). Descriptive statistics were performed by calculating frequencies, percentages, means, and standard deviations. We compared maternal and neonatal characteristics of the study population using Mantel-Haenszel chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. A significant difference was assumed when P < 0.05. We compared the overall and cause-specific mortality rates (numbers of deaths per 1,000 live births) among infants born in two birth-year periods (2010-2012 and 2013-2015.) We selected comparisons between the two birth-year periods instead of individual birth years to provide a sufficiently large sample to control for confounding factors in our analysis and to provide mortality estimates with greater precision.

3. Results

Characteristics of the study population

171 infants enrolled in the study, 91 (53.2%) of whom were male (Table 1). 100 of the infants (58.4%) were singletons. The mean birth weight and gestational age were 733.5 grams and 24.9 weeks, respectively. The majority of mothers (125, 69.3%) had antenatal care at KFMC, and 57 (33.3%) were primigravidas. 85 babies (49.7%) were born by cesarean section, and 162 (94.7%) received steroids. Surfactants were administered to 141 (82.4%) infants.

We detected an increase in the number of normal vaginal deliveries in the second period (45 compared to 41 deliveries during the first period) (P = 0.037). There was also a higher percentage of babies receiving surfactants (72 [74%] vs. 69 [90.3%]) (P = 0.014). There were no significant changes in gestational age, sex, antenatal care, and prenatal glucocorticoid administration. The mean gestational age was lower during the second period (24.4 vs. 25.5) (P = 0.0352). The mean birth weight was also lower during the second period (776.5 ± 0.321 vs. 690.9 ± 0.623) (P < 0.001).

Changes in overall mortality

The overall mortality rate did not change significantly from 2010-2012 to 2013-20015, but we detected a decreased by 14.6% from 432 (CI: 354-519) to 369 (CI: 286-452) deaths per 1,000 live births. There were no significant changes between the two periods in the numbers of patients with DNR status, due to either severe IVH or lethal congenital anomalies.

Changes in cause-specific mortality

The leading causes of death were prematurity, which occurred in 49 infants (28.6%), sepsis, which occurred in 36 infants (21%), and respiratory distress syndrome (RDS), which occurred in 20 infants (11.6%) (Table 2). Overall, the number of deaths per 1,000 live births attributed to prematurity increased during the second period by 54.9% from 91 (CI: 51-131) to 141 (CI: 90-192). The death rate due to IVH increased by 8.3% from 36 (CI: 11-62) to 39 (CI: 12-66). Deaths due to sepsis reduced by 40% from 105 (CI: 62-157) during the first period to 63 (CI: 29-97) during the second period. Likewise, mortality due to RDS reduced by 42.3% from 59 (CI: 27-91) to 34 (CI: 9-59), and that due to pulmonary hemorrhage reduced by 17% from 41 (CI: 14-68) to 34 (CI: 9-59). Changes over time in the frequencies of deaths attributed to necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), congenital anomalies, and unknown causes were not statistically significant.

Table 2: Causes of death from 2010-2015

Year	**2010-2012**	**2013-2015**	**P value**
Total live births	220	206	
Total deaths	95	76	
Cause-specific mortality rate per 1,000 live births			
Prematurity¶	91 (51-131)	141 (90-192)	0.1294
RDS¶	59 (27-91)	34 (9-59)	0.2320
Pulmonary hemorrhage¶	41 (14-68)	34 (9-59)	0.7123
BPD¶	18 (0-36)	10 (-4-23)	0.4615
IVH¶	36 (11-62)	39 (12-66)	0.8954
NEC¶	18 (0-36)	15 (-2-31)	0.7709
Sepsis¶	105 (62-147)	63 (29-97)	0.1415
Congenital anomalies¶	23 (3-43)	10 (-4-23)	0.2949
Other¶	9 (-4-22)	15 (-2-31)	0.6024
Unknown¶	32 (8-55)	10 (-4-23)	0.1167

Cause-specific death rate/1,000 live births (95% confidence interval [CI]); BPD = bronchopulmonary dysplasia, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, RDS = respiratory distress syndrome.

Causes of death according to gestational age

We observed that, in infants born at 23-24 weeks, the most common single cause of death was prematurity, which accounted for 54% of total deaths (Table 3). This was followed by IVH and sepsis (12.1% each), and RDS (8.1%). In infants born at gestational ages of 25-26 weeks, sepsis was the leading cause of death (35.3%). This was followed by RDS, pulmonary hemorrhage, and prematurity (13.7% each. In infants born at 27-28 week, sepsis again accounted for the majority of deaths (20%), while RDS accounted for 15.5%, congenital anomalies and unknown causes accounted for 13.3%.

Forty infants were born at 23 weeks. Thirty-seven of these infants (92.5%) died. The majority of these infants died due to prematurity (64.8%). Prematurity was responsible for 74%, 46.9%, 27.7 %, 28.4%, and 19% of deaths in infants born at 24, 25, 26, 27, and 28 weeks, respectively.

Table 3: Causes of death according to the gestational week

Cause of death	23 Week	24 Week	25 Week	26 Week	27 Week	28 Week
Live births	40	50	49	101	102	84
Total deaths (%)	37 (92.5)	37 (74.0)	23 (46.94)	28 (27.72)	29 (28.43)	16 (19.05)
Causes						
Prematurity (%)	24 (64.86)	16 (43.24)	3 (13.04)	4 (14.28)	1 (3.45)	1 (6.25)
RDS (%)	2 (5.40)	4 (10.81)	3 (13.04)	4 (14.28)	3 (10.34)	4 (2.5)
Pulmonary hemorrhage (%)	2 (5.40)	2 (5.40)	4 (17.39)	3 (10.71)	5 (17.24)	0
BPD (%)	1 (2.7)	2 (5.40)	0	1 (3.57)	0	2 (12.5)
Sepsis (%)	2 (5.40)	7 (18.91)	10 (43.7)	8 (28.57)	6 (20.68)	3 18.75)
NEC (%)	1 (2.70)	1 (2.70)	0	2 (7.14)	2 (6.89)	1 (6.25)
IVH (%)	5 (13.51)	4 (10.81)	2 (8.69)	4 (14.28)	1 (3.44)	0
Congenital anomalies (%)	0	0	0	0	5 (17.24)	2 (12.5)
Other (%)	0	0	0	1 (3.5)	2 (6.89)	1 (6.25)
Unknown (%)	0	1 (2.7)	1 (4.34)	1 (3.57)	4 (13.79)	2 (12.5)

BPD = bronchopulmonary dysplasia, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, RDS = respiratory distress syndrome.

4. Discussion

We found a relative reduction in the death rate among extremely premature infants born at KFMC between 2010 and 2015. The decrease in the overall mortality rate was 14.6% less in second period compared to the first period. More than half of the decrease in overall mortality was accounted for by a reduction in deaths attributed to Sepsis and respiratory distress syndrome. Patel et al. (2015) found similar results in a multicenter study early in 2015 in the United States. This trend can be attributed to more frequent use of surfactants and better ventilator strategies used in extremely preterm infants, as well as the implementation of strict infection protocol procedures in our unit. Deaths attributed to prematurity and IVH had an increasing trend in 2013-2015 compared to Patel et al.'s findings, as they reported fewer deaths attributed to prematurity and no significant difference in deaths due to central nervous system injury or IVH. This may be because of the increased number of infants born at 23-24 weeks during that period ($P = 0.0352$) as well as having lower birth weights ($P < 0.001$). There were no significant changes in the number of deaths attributed to BPD or NEC, although Patel et al. (2015) found more deaths due to NEC and fewer deaths due to BPD. Deaths attributed to congenital anomalies and unknown causes were not significantly changed between the two periods. This finding is consistent with those of the previously mentioned study. Even though there was no change in the number of deaths due to unknown causes, there was a trend for more accurate and clear entries of the causes of death in our study.

Improved overall survival of premature infants has recently been reported by researchers from the Canadian Neonatal Network (Shah, 2012) and the Vermont Oxford Network (Horbar, 2009), although these studies did not evaluate changes in cause-specific mortality. The observed decline in overall mortality in our study is thought to be a result of the mandatory enrollment of Neonatal registrars and fellows in the Neonatal Resuscitation Program, this observation was reported in a study conducted in China by Zhu et al. (1997).

Our study has some limitations. First, the size of the study population was small. Second, the study had a retrospective design. Third, there may be concerns regarding our use of a single underlying cause of death as a means of investigating and evaluating infant mortality. The use of the single underlying-cause-of-death model ignores the roles of other causes and their contributions to death. Thus, its reliability may be adversely affected, as disease evaluation and coding tend to vary among physicians and other health providers (Kistantas, 2008). Variations in opinions among individuals responsible for "coding" a condition or a disease can affect the accuracy of the classification system (Nam, 1989). For instance, death due to prematurity and that due to respiratory distress syndrome may be classified differently by different individuals. We noticed a non-significant decreased in the rate of mortality due to unknown causes; this may have been due to the ability of the physicians to better identify and code the different causes of death after receiving an ongoing training over the time of our study. A similar finding was also observed in a research study done in Fiji in 2013 (Rampatige, 2013).

5. Conclusions

The overall rates of death and those specifically attributed to sepsis, RDS, and pulmonary hemorrhage were reduced among extremely premature infants, while deaths attributed to prematurity and IVH increased. There were no significant changes in the numbers of deaths due to NEC, BPD, and congenital anomalies. When counseling families, it is preferable to acquaint them with the outcome of our unit and prepare them for the expected consequences.

The underlying causes of death should be clearly identified in infants' charts. This requires better training of physicians to ensure complete data entry and practice accurate coding. In conclusion, more multicenter, prospective studies should be conducted to facilitate a better understanding of the causes and trends of death in extreme premature infants. Therefore, developing and implementing strategies against the potentially lethal complications of premature birth.

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