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Research Article

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Mortality Predictive Risk Factors of Limits-Of-Viability Preterm Infants at 23 And 24 Weeks Gestation

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Abstract

Objective: *The purpose of this study was to examine perinatal and postnatal events associated with neonatal mortality among 23 and 24 weeks gestation preterm infants.*

Methods: *A population-based retrospective study of infants born at 23 and 24 weeks gestational age over a two-andhalf- year period.*

Results: *A hundred and five preterm infants were investigated during the period of the study: 60 infants born at 23 weeks gestation and 45 infants born at 24 weeks gestation. In total, 79 infants were admitted to the NICU (75%). Twenty-six infants died in the delivery room. Twenty-six infants died within the first two weeks of life (33%) and 12 died beyond the first two weeks of life (15%). The survival rates for infants admitted to the NICU were 35% and 66% for 23 and 24 weeks infants, respectively. Altogether, 41 of all NICU-admitted infants remained alive until discharge (52%). (Figure 1) The majority of deaths occurred during the first two weeks of life (26/38; 68%).Tthe most associated risk factors were a lack of antenatal steroid (p value < .001), bruises (0.002), gelatinous skin (0.032), and IVH (0.03) . Severe respiratory failure was the main cause of death.*

Failure to extubate from a respirator by two weeks of age with an FIO_2 requirement > 50% was the main risk factor associated with death beyond two weeks of life (OR > 10.0 and p value of< 0.001).In comparison to mothers who did not receive antenatal steroids, an incomplete course showed a significant but lower risk of mortality (OR=3 vs. 13 and P value 0.001 vs 0.3). The rate of ANS administration approached 90% in 24 weeks gestation age vs 53% in the 23 weeks age group. The tendency to perform CS was < 10% in 23 weeks and up to 28 % in 24 weeks. Attending neonatologists decided to offer resuscitation in 93 % of 24 weeks versus 65% of 23 weeks newborn.

Conclusions: *Antenatal steroids, the degree of immaturity, a birth weight less than 750 grams, and need for IPPV ventilation while requiring more than 50% FIO2 at two weeks of age were the circumstances most associated with death. The survival rates until discharge for 23 and 24 weeks gestational age infants were 35% and 66%. Resuscitation selection criteria for 23 weeks gestation would provide a reasonable platform for forming an approach towards this particular gestational age.*

Keywords: Limit of Viability, Extremely Preterm, 23, 24 Weeks Gestation Age, Mortality Rate, Outcome, Complications, Risk Factors, Death

CI : Confedince interval
DR : Delivery room
ELBW : Extremely Low Birth weight
NICU : Neonatal intensive care unit
OR : Odds ratio
PIE : Pulmonary Interstitial Emphysema
VD/CS: Vaginal delivery/Cesarean section
WWRC: Women's Wellness and research center

Introduction

One of the most challenging moments in a tertiary NICU occurs when a limits-of-viability infant is about to be delivered. Those moments are overwhelming not only for the parents but also for the NICU staffs, who need an encyclopaedic knowledge of the scale of resources to support those critical gestational age infants. The average length of stay until discharge is estimated to be between 110 and 140 days. The average daily cost of an NICU bed is around 1392 USD per day (excluding staff wages). An extremely premature baby costs an average of 62,000 USD during hospitalization in the WWRC depending on the gestational age. International figures are around the same amount [1, 2].

Embryologically, limits-of-viability newborn body organs are resting in developmental stages, which does not empower them to function appropriately and thus they struggle to meet the extra uterine ultimatum. In every station of their life, several risk factors contribute to death or severe morbidity, such as antenatal/perinatal factors, delivery room circumstances, and the NICU stay. Those two gestational ages are often considered to be the lower end of foetal viability [3-5].

The mortality rate and level of morbidity in many centres suggest a critical question: how, why, and when do those infants survive inside a tertiary NICU? Some prior studies have suggested that 90% of ELBWinfants' mortality occurs within the first 28 days; most occur within the 72 hours after birth [3-5]. Patel et al. demonstrated that 68% of limits-of-viability infants die with the first two weeks of life.

Our hospital is a state-of-the-art tertiary referral women's hospital where 40 to 50 deliveries occur daily. The WWRC accommodates 214 maternity beds and 110 NICU cots distributed across two floors. The WWRC is a referral hospital for three governmental and five private maternity services. In 2004 and 2005, 12 infants at 23 weeks gestation were admitted to our NICU and only one baby survived to discharge (9%). Since 2009, we have been encouraged to admit infants of this gestational age to our NICU, but the cumulative survival rate over 10 years has not exceeded 18%, with an average length of stay is 140 days for those who survived. This study analyses the risk factors associated with mortality among those two gestational ages and identifies those infants with a slim chance of survival to improve physicians' decision making and encourage more informative communication with parents. We measure the probability of death before and after introducing the resuscitation score (the score of seven) targeting the 23 weeks gestational age.

Methods

This population-based retrospective study was designed to assess the mortality and survival rate of all ELBW infants born at 23 and 24 weeks gestation delivered among the residents of Qatar in the WWRC from 2016 to 2018. We evaluated the outcomes of these infants after introducing the resuscitation guideline concerning the limits of viability for 23 and 24 weeks gestation infants and a dedicated a special well equipped separate unite catering only ELBW infants less than 28 weeks. We retrieved the data from the medical records of each infant, the Pearl-Peristat Maternal and newborn registry and Vermont Oxford database related to our hospital. We defined cases as live-born at 23 weeks plus zero days to 24 weeks plus six days who were born, died, or admitted to the NICU. The estimation of gestational age was verified from the maternal ultrasound, in vitro fertilization dates, first-trimester ultrasound, and/or menstrual dating confirmed by second-trimester ultrasound. The study excluded confirmed intrauterine fetal death and infants with significant anomalies. The rate of NICU admission, death before two weeks of age, and death before discharge were assessed. In this study, we also evaluated complications during the first two weeks associated with death to measure the probability of dying when such complications occurred.

We performed a univariate analysis to calculate the crude OR, comparing cases and controls for each potential risk factor. All statistically significant ($P<0.05$) variables from the univariate analysis and potentially clinically relevant and previously cited risk factors were entered into a multivariate logistic regression model. All statistical analyses were performed using SPSS software version 21.0 (SPSS, Inc, Chicago, Ill).

Results

A hundred and five preterm infants were investigated during the period of the study: 60 infants born at 23 weeks gestation and 45 infants born at 24 weeks gestation. In total, 79 infants were admitted to the NICU (75%). Twenty-six infants died in the delivery room. Twenty-six infants died within the first two weeks of life (33%) and 12 died beyond the first two weeks of life (15%). The survival rates for infants admitted to the NICU were 35% and 66% for 23 and 24 weeks infants, respectively. Altogether, 41 of all NICU-admitted infants remained alive until discharge (52%). (Figure 1) The majority of deaths occurred during the first two weeks of life (26/38; 68%). the most associated risk factors were a lack of antenatal steroid (p value < .001), bruises (0.002), gelatinous skin (0.032), and IVH (0.03) . Severe respiratory failure was the main cause of death.

Failure to extubate from a respirator by two weeks of age with an FIO2 requirement > 50% was the main risk factor associated with death beyond two weeks of life (OR > 10.0 and p value of< 0.001). In comparison to mothers who did not receive antenatal steroids, an incomplete course showed a significant but lower risk of mortality (OR=3 vs. 13 and P value 0.001 vs 0.3). The rate of ANS administration approached 90% in 24 weeks gestation age vs 53% in the 23 weeks age group. The tendency to perform CS was < 10% in 23 weeks and up to 28 % in 24 weeks. Attending neonatologists decided to offer resuscitation in 93 % of 24 weeks versus 65% of 23 weeks newborn. The mode of the delivery, number of surfactant doses, blood transfusion were not associated with increase risk of death. (table 1 & 2) Maternal infection prior to birth and no antibiotics administered within one week before birth was associated with early death (table 1).

Discussion

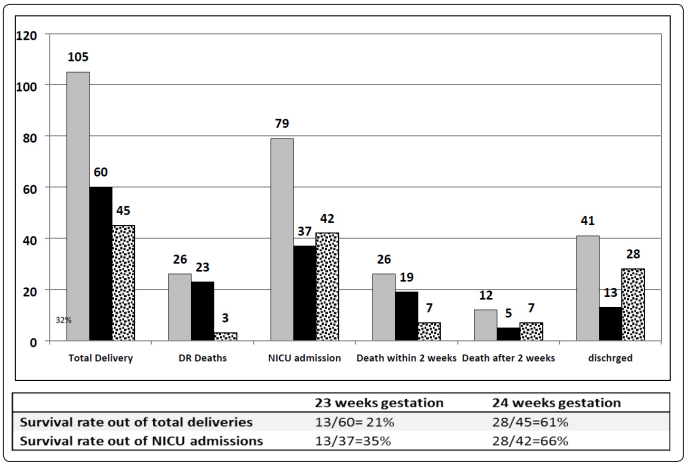
Managing ELBW infants born at 23 and 24 weeks gestation has significant psychological, clinical, and administrative load along with high expectation from society owing to the influence of the media. The magnitude of social disruption in parents' life is unbearable. It also provides a rich platform for ethical dilemmas and medico-legal conflicts between parents and caregivers. In this study, we attempted not only to report the survival and mortality rates and the associated circumstances but also to understand the impact of different events on two gestational ages with the highest mortality rate recorded in any busy referral NICU. There is a significant improvement in the survival of 25 weeks and beyond infants because of advanced technology, the introduction of surfactants/antenatal steroids, gentler ventilation modes, strict infection control, DR golden hours, and adequate nutritional support for those age groups. However, 23 and 24 weeks gestation survival lags behind those infants born at 25 weeks and beyond. Costello et al [6]. compared the survival rates of ELBW infants born in 1995 and 2006 and found a 10% improvement in the survival of the 23 and 24 weeks gestational age groups [7]. Thomas et al., in a small sample size cohort, reported a survival rate of 33% for 23 weeks gestation [8]. On the other hand, some investigators have found considerably higher survival on discharge from the NICU for both 23 weeks gestation (65%) and 24 weeks gestation (78%) [8]. Nozomi et al. demonstrated different survival rates among other large cohort studies, fluctuating between 36% and 65% in 23 weeks gestation and up to 98% in 24 weeks gestation.

In this study, the rate of admission to the NICU was 11% higher for both gestational ages than that reported by Costello et al. [9, 10].

The recorded survival rates in our institute are 35% and 66% until discharge for 23 and 24 weeks, respectively. Those two figures are consistent with those in several developed countries: between 20% and 60% for 23 weeks gestation and as high as 75% for 24 weeks gestation [9-12,13].

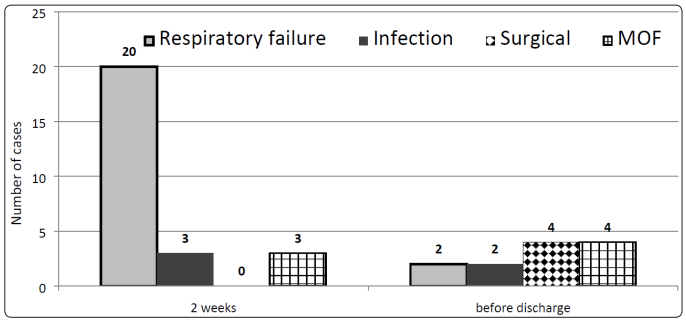
Among 23 weeks gestational age infants, 23 (38%) either died during DR resuscitation or resuscitation was not attempted because of the severe immature status or parents' wish. However, for 24 weeks gestation, the vast majority of newborns were resuscitated until NICU admission except in three of 45 cases (6%). The study's objective was to explore the possibility of making an early decision to continue care by studying the potential risk factors associated with early death and help with parent counselling regarding the survival of their infants. We chose to compare two weeks against until discharge because during the first two weeks of life, the vast majority of complications attributed to prematurity should be declared during this period apart from infections and surgical emergencies. Death during the first two weeks was high among those newborns whose mothers did not receive antenatal steroids, showed significant signs of immaturity (gelatinous skin, bruises, and fused eyes), needed mechanical ventilation at two weeks of life with FIO2 higher than 50%, and a birth weight less than 750 grams. The infants developed IVH grades III and IV were at more risk of dying, but mostly after two weeks of age. Early pneumothorax and pulmonary haemorrhage were potential risk factors for death, but after two weeks of age, which might indicate the lung damage left after those two complications. While, a completed antenatal steroid course was associated with a better outcome, the incomplete course still carries a lower risk of death than infants with no antenatal steroids in 23 weeks gestation (OR=2.7 vs. 13; P<0.001) and in 24 weeks gestation (OR=2.03 and 2.89; P=0.06).

Our study represents a 3 years single-centre experience with an aggressive approach towards antenatal, perinatal, and neonatal intervention. Our data support the use of antenatal steroids, even an incomplete course. The protective effect of antenatal antibiotics before delivery supports the fact that infection is a leading cause of premature birth. Every effort to wean infants from mechanical ventilation and use lower FIO_2 can improve the survival of those two gestational ages. Negative findings should be treated with caution.



	23 weeks gestation	24 weeks gestation
Survival rate out of total deliveries	13/60= 21%	28/45=61%
Survival rate out of NICU admissions	13/37=35%	28/42=66%

Figure 1: The Sample distribution: total deliveries, DR deaths, number of NICU admission, newborns died within the first 2 weeks, those died after two weeks and newborns lived till discharge (105 infants)



MOF= multiorgan failure.

Figure 2: Primary causes of death.(38/79)

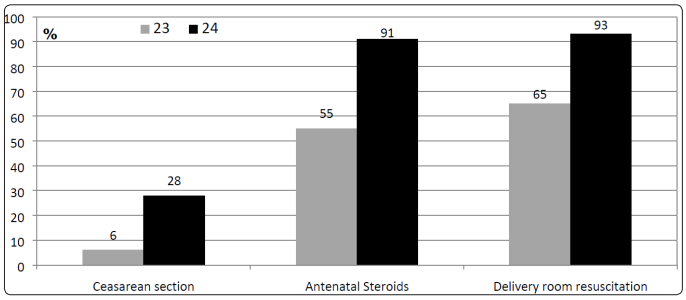


Figure 3: Intervensions and pproach to Infants Born at 23 to 24 Weeks' Gestation:

Table 1: 23 weeks and 24 weeks deaths within 2 weeks including labor room deaths

		ALL INFANTS	
		OR 95% C. I	P value
Maternal infection	**No**	0.57 (0.22 -1.514)	0.261
Maternal Antibiotics	No	1.88 (0.72-4.916)	0.196
	Yes	Ref	
Antenatal steroids	None	15.86 (3.95-63.69)	<.001
	Incomplete	3.083 (.898-10.586)	0.074
	Complete	Ref	
Mode of delivery	NVD	Ref	
	CS	0.446 (0.11-1.74)	0.246
Bruises	Yes	6.86 (1.99-23.64)	0.002
Gelatinous skin	Yes	3.83 (1.12-3.08)	0.032
Fused eyes	Yes	2.88 (.90-9.17)	0.074
Birth weight	≤750g	1.57 (0.39-6.36)	0.529
	≥751g	Reference	
Surfactant doses	1 dose	Reference	
	≥ 2 doses	1.58 (0.53-4.741)	0.411
Blood transfusion	No	Reference	
	Yes	0.25 (.090-.695)	0.008
IVHgrade3or4	No	Ref	
	Yes	1.97 (.548 - 7.087)	0.0299
Chorioamnionitis	No	Ref	
	Yes	0.69 (0.2 - 2.44)	0.569

Only risk factors with a significant p-value were entered into logistic regression. Significant p value < 0.05.

Table 2: Patient's risk factors associated with Neonatal mortality before discharge: 79 infants that admitted to NICU

Risk factors	Number of cases	Numbers of Deaths / total number of NICU admissions	%	OR	95% CI	P-value for OR
Failure to extubate from IPPV by the 2nd week of life and >50% FIO2	(26)	25/75	34.7	97.500	11.749-809.10	<0.001
Completed course of ANS	(44)	15/79	19	Reference		
Incomplete course of ANS	(19)	9/79	11.4	1.74	0.582-5.202	0.3
No ANS	(16)	14/79	17.7	13.533	2.712-67.528	0.001
Gelatinous skin	(17)*	13/51	25.5	3.656	0.99-13.516	0.0489
Bruises	(21)*	17/52	32.7	7.727	2.076-28.765	0.002
Fused Eyes	(19)	13/53	24.5	2.437	.750-7.922	0.14
Birth weight ≥ 751	(12)*	4/79	5.1	Reference		
Birth weight ≤750	(67)*	34/79	43	2.061	.566-7.503	0.2
Pulmonary Hemorrhage	(10)*	7/74	9.5	3.000	.711-12.660	0.14
PIE	(22)	12/74	16.2	1.513	.556-4.121	0.41
Pneumothorax	(3)*	2/74	2.7	2.437	.211-28.121	0.475
IVH III / IV	(13)	9/67	13.4	4.5	1.218-16.622	0.024
All Maternal infections	(34)	12/78	15.4	0.378	0.15-0.952	0.039
Chorioamnionitis	(15)	6/79	7.6	0.667	.213-2.091	0.5
Maternal antibiotics	(40)	17/76	22.4	0.591	.238-1.467	0.26
Vaginal delivery	(64)	33/79	41.8	Reference		
Caesarean section	(15)	5/79	6.3	0.470	.144-1.529	0.209
1 dose of Surfactant	(25)	11/73	15.1	Reference		
≥2 doses of surfactant	(48)	23/73	31.5	1.171	0.443-3.094	0.8
Blood transfusion	(45)	18/75	24	.444	.173-1.141	0.092

Variables*= Fisher's exact
Chi-Square for contingency tables: is there an association between risk factor and death?

Logistic regression: Can we quantify the association, The odds ratio is a measure of effect size, describing the strength of association.

Only risk factors with a significant p-value were entered into logistic regression. Significant p value < 0.05 OR > 1 = higher odds, OR < 1 = reduced /lower odds .The odds ratio is only significant if: the p-value is <0.05 and Its 95% CI does not span 1.

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