Early outcome of preterm infants with birth weight of 1500 g or less and gestational age of 30 weeks or less in Isfahan city, Iran

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Original article

Background: **The outcome of preterm neonates has been varied in different hospitals and regions in developing countries. This study aimed to determine the mortality, morbidity and survival of neonates weighing 1500 g or less and with gestational age of 30 weeks or less who were admitted to referral neonatal intensive care units (NICUs) of two hospitals in Isfahan city, Iran and to investigate the effect of birth weight, gestational age and Apgar score on infant mortality.**

Methods: **We studied retrospectively the morbidity, mortality and survival of 194 newborns with a birth weight of ≤1500 g and a gestational age of ≤30 weeks who had been hospitalized during a 15-month period in NICUs of the two referral hospitals. The Kaplan-Meier method was used to estimate the survival of the neonates. The survival was defined as the discharge of live infant from the hospital within 75 days.**

Results: **Overall, 125 (64.4%; 95%CI 58%-71%) of the 194 infants died during their hospital stay. The morbidity in this study was as follows: respiratory distress syndrome 76% (95%CI 70%-82%), septicemia 30.9% (95%CI 24%-37%), bronchopulmonary dysplasia 10.3% (95%CI 6%-15%), necrotizing enterocolitis 6.7% (95%CI 3%-10%), patent ductus arteriosus 12.4% (95%CI 8%-17%), intraventricular hemorrhage 7.2% (95%CI 4%-11%), and apnea 16.5% (95%CI 11%-22%). Packed cell transfusion was required in 43.3% (95%CI 36%-50%) of the neonates. The Kaplan Meier survival analysis revealed that 75% of the infants would live past 2 days, 50% after 14 days, and 25% after 69 days.**

Conclusions: **Even with modern perinatal technology and care, early deaths of very low birth weight infants are still common in our referral hospitals. The outcome of infants born at 24-28 weeks is unfavorable. The hospital level is an important factor affecting the mortality and morbidity of these infants.**

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Introduction

Prematurity is the most common cause of neonatal death worldwide, and it causes 60%-80% of deaths of infants without congenital abnormality. [1] The improvement in survival rates of preterm and very low birth weight (VLBW) infants has been well documented during the last 20 years.[2,3] More recently, a marked reduction in the mortality rate has been reported following the introduction and widespread use of antenatal steroids and exogenous surfactant.[4] However, survival and outcome of preterm neonates in different hospitals and regions vary widely. Hence the outcome study of preterm infants in each population and region is essential in developing countries.[4]

With further understanding of the disease process and the development of new therapies, surveillance of up-to-date outcome of the patients would be essential in monitoring the effectiveness of current practice.[5] Although there is increasing evidence that mortality and later morbidity in high-risk infants are more closely related to gestational age rather than to birth weight,[6-8] a combination of both variables may give an even more accurate prediction of outcome once the infant is born.[9]

The aim of this study was to determine neonatal

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morbidity and mortality of babies weighing 1500 g or less and with a gestational age of 30 weeks or less. In addition, the Kaplan-Meier method was used to investigate the neonatal survival.

Methods

This retrospective study was conducted in the neonatal intensive care units (NICU) of the two only referral hospitals (Alzahra and Shahid Beheshi) in Isfahan city (the second largest city in Iran) over a period of 15 months from January 2005 to March 2006.

The outcome measure was the number of inhospital deaths. Survival was defined as the discharge of live infants from the hospital within 75 days.

All newborns weighing 1500 g or less and with a gestational age of 30 weeks or less who were admitted to the aforementioned NICUs were included in the study. Newborns with congenital anomalies and those who were discharged voluntarily by their parents were excluded from the study. Data collected included birth weight, gestational age (New Ballard Score),[10] 5th minute Apgar score, details of morbidities and mortalities during hospital stay, if any.

Statistical analysis

SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL) was used for data analysis. The Kaplan-Meier method was used to estimate the survival of infants during the hospital stay, and the survival function from life-time data. In medical research it might be used to measure the fraction of patients living for a certain amount of time after treatment. A plot of the Kaplan-Meier estimate of the survival function is a series of horizontal steps of declining magnitude which, when a large enough sample is taken, approaches the true survival function for that population.[11]

Infant's survival during the first 75 days of life was estimated using a generalized linear model with binomial family and logit link. The survival probability was estimated by the following formulae using birth weight (BW), gestational age (GA) and Apgar score (AS):

$$\text{Survival probability}=\frac{1}{1-\exp[-14.28+0.24(AS)+0.39(GA)+0.001(BW)]}$$

The survival probability of infants, based on Apgar score, GA, BW and hospital stay period (HP) in days, was as follows:

$$\text{Survival probability}=\frac{1}{1-\exp[-24.32+0.14(AS)+0.0008(BW)+0.091(HP)]}$$

$\text{Exp}(a) = e^{a}$

e = neper number

Results

During the study period, 194 NICU admissions of infants with birth weight ≤1500 g and gestational age ≤30 weeks were documented. Of them, a total of 125 (64.4%; 95%CI 58%-71%) died during the hospital stay. The increase of birth weight and gestational age was associated with the decline of mortality (Table 1). Overall 49 of 81 girls (60.9%, 95%CI 50%-71%) and 76 of 113 boys (67.3%, 95%CI 55%-80%) died (P>0.05). The higher mortality rate in males than in females was not statistically significant.

The data of delivery route were available in 171 infants, and 43 (70.5%) of 61 (95%CI 59%-82%) infants born by normal vaginal delivery and 67 (60.9%) of 110 (95%CI 52%-72%) neonates born by cesarean section died. There was no significant difference in the mortality rate of infants born through vaginal delivery or cesarean section.

The data of Apgar score were available for 162 infants. Overall, 72.1% (95%CI 63%-83%) of newborns with first minute Apgar score ≤5/10 and 42.1% (95%CI 28%-56%) with Apgar score >5/10 died (P<0.05); 78.5% (95%CI 69%-88%) with 5 minute Apgar score <7/10, and 52.2% (95%CI 42%-63%) with Apgar score ≥7/10 died (P=0.001).

Neonatal illnesses were documented in 194 infants (Table 2). The most frequent illness was respiratory distress syndrome (RDS) while necrotizing enterocolitis (NEC) had the lowest frequency. Central vein catheter (CVC), umbilical artery catheter (UAC) and umbilical vein catheter (UVC) were used in 8 (4.1%, 95%CI 1%-7%), 44 (22.7%, 95%CI 17%-29%) and 23 (11.9%, 95%CI 7%-16%) of the 194 infants respectively. The mortality rate in infants without catheters was 52.9% (95%CI 50%-66%). The mortality rate in infants with UAC and UVC was 86.4% (95%CI 76%-97%) and 91.3% (95%CI 79%-100%) respectively, which were significantly higher than those in the first group (P<0.05). The mortality in infants with CVC was lower than that in those without a catheter (37.5%) (P>0.05). The mortality in the UAC and UVC groups was not

Table 1. Neonatal mortality by birth weight and gestational age

Variables	Number of infants	Number of deaths (95% CI)
Birth weight (g)		
400-750	34	30 (77%-100%)
751-1000	73	52 (61%-82%)
1001-1250	54	29 (40%-67%)
1251-1500	33	14 (25%-60%)
Gestational age (wk)		
24-27	48	42 (78%-97%)
27-28	74	51 (58%-80%)
28-30	72	32 (33%-56%)

Table 2. Neonatal morbidity and mortality in very low birth weight infants

Illness	Frequency of morbidity, 95%CI	Mortality rate, 95%CI (%)	Incidence in dead babies, 95%CI (%)
Respiratory distress syndrome	148 (70%-82%)	72.3 (65-80)	55.2 (48-62)
Septicemia	60 (24%-37%)	56.7 (44-70)	17.5 (12-23)
Apnea	32 (11%-22%)	78.1 (63-93)	12.9 (8-18)
Patent ductus arteriosus	24 (8%-17%)	66.7 (46-87)	8.2 (4-12)
Bronchopulmonory dysplasia	20 (6%-15%)	20 (1-39)	2.1 (1.5-2.7)
Intraventricular hemorrhage	14 (4%-11%)	57.1 (27-87)	4.1 (1-7)
Necrotizing enterocolitis	13 (3%-10%)	76.9 (50-100)	5.2 (2-8)

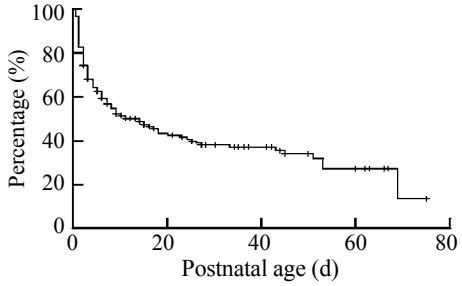

Fig. Survival analysis curve analyzed by the Kaplan-Meier method.

significantly different (P>0.05) but in the CVC group it was lower than that in the other groups. The statistical test was not valid because of the low frequency of CVC.

Overall, 148 of the 194 babies had RDS, of whom 78 (52.7%, 95%CI 45%-61%) received surfactant therapy, and the mortality in this group was 82.1% (95%CI 73%-91%) and in those who did not receive surfactant therapy, the mortality rate was 61.4% (95%CI 50%-73%). The mortality rate was significantly higher in those who received surfactant therapy (P<0.05).

In 101 (52.1%, 95%CI 45%-59%) infants who received ventilator, the mortality was 81.2% (95%CI 73%-89%) and in babies who did not receive ventilator, the mortality rate was 46.2% (95%CI 36%-57%) (P<0.05).

Packed cell transfusion was required in 43.3% (95%CI 36%-50%) of the neonates. The mortality rate in these babies was 63.1% and in babies without transfusion was 65.5% (P>0.05).

Sixty-one (31.4%, 95%CI 25%-38%), 3 (1.5%, 95%CI 0%-3%), 35 (18%, 95%CI 13%-24%) and 1 (0.5%, 95%CI 0%-2%) of mothers had premature rupture of membranes, eclampsia, pre-eclampsia and chorioamnionitis, respectively.

The mortality rate of infants was investigated with the Kaplan-Meier method. The average age at the time of death was 28.9 days, with standard error of 2.6 days (95%CI 23.8-34). The median of mortality with standard error of 3.2 days was 14 days (95%CI 7.7-20.3). It is expected that 75% of infants would survive after 2 days, 50% after 14 days, and 25% after 69 days (Fig.).

Gestational age had the highest effect on survival with odds ratio of 1.472. Apgar score with odds ratio of 1.267 had greater effect on survival than birth weight did with odds ratio of 1.001. The mean gestational age in neonates of Alzahra NICU was 27.95 weeks and in neonates of Shahid Beheshti NICU was 27.8 weeks (P>0.05). The mean birth weight in neonates of Alzahra NICU was 1027 g and in neonates of Shahid Beheshti NICU was 986 g (P>0.05).

Discussion

Neonatal death is a serious concern both in developing and developed countries. While infant mortality rates have been decreasing steadily worldwide, changes in neonatal mortality rate have been much slower.[12] Consistent with a study demonstrating that 34% of infant deaths occurred in premature infants born before 32 weeks of gestation with birth weight ≤1500 g,[13] in our study the most common causes of neonatal mortality were prematurity and low birth weight. We found a mortality rate of 64.4% (95%CI 58%-71%). The mortality rate in our study was significantly higher than that in other studies reporting a prevalence of 23%-78%,[4,14-19] and this might be due to the exclusion of neonates with a gestational age greater than 30 weeks. In our study however, the mortality rate among neonates with gestational age of 29-30 weeks was still higher than in other studies. For instance in Finland this rate is less than 20%[4] and in Canada it is less than 5%[5] but in our study it is 44.4%.

Studies on mortality and outcome of VLBW infants are usually based on NICU patient cohorts and thus they do not represent the complete birth cohort.[4] Hence, they do not include the mortality of the neonates in delivery room or in hospitals without NICU. So it is probable that real neonatal mortality would be higher than the reported mortality in NICUs. However in some studies neonates who died in the delivery room or within 12 hours of life were excluded from the study as intrauterine causes are more likely to be the factors of death in these cases.[12]

Our inclusion criteria included a birth weight ≤1500 g and a gestational age of ≤30 weeks. A birth weight based inclusion criterion is often criticized because mortality and morbidity are more related to gestational age than to weight but the commonly used birth weight based criterion facilitates comparisons with other studies and is applicable for a nationwide study.[4]

The frequency of neonatal illness in our study is similar to that reported by other studies. In other studies the prevalences of RDS, septicemia, bronchopulmonary dysplasia, NEC, patent ductus arteriosus and intraventricular hemorrhage are 43%-76%, 22%-34%, 14%-39%, 7%-35%, 34%-44%, and 3%-27% respectively.[4,17,18,20,21]

The Kaplan-Meier method was used to assess the survival of VLBW infants in Bangladesh; it was 50% at the second day of hospital stay and 25% on the 14th day of hospital stay.[19] The survival rate of neonates born on 24-30 weeks at the 14th day of hospital stay in Germany was reported to be more than 80%.[22] The survival rate of neonates in our study was about 50% on the 14th day of hospital stay. Consistent with the rates reported by other studies, the mortality declined with increase in birth weight, gestational age and Apgar score.[12]

A study documented higher mortality in male neonates,[5] and in the present study the mortality rate was also higher in males (67.3%) than in females (60.9%), though the difference was not statistically significant, but it might be of clinical importance. In our study the mortality rate in babies delivered by normal vaginal delivery was about 10%, higher than those delivered by cesarean section. This may be of clinical concern, but is not statistically significant. Vaginal delivery was reported to be significantly associated with intraventricular hemorrhage,[4] and some other studies[23,24] found the lower VLBW mortality rate of those delivered by cesarean section.

The varied survival rates of VLBW infants are dependent upon resources and experience of NICU care.[25,26] Increased infant mortality is associated with substandard neonatal care and early neonatal factors.[22] In our study, the mortality of the two NICUs under study was significantly different. The NICU care is usually well defined on the basis of nursing staff and technical equipment, as well as neonatal conditions such as gestational age, multiplicity or requirement for ventilator support.[27-29]

We did not document any significant difference in the mean gestational age or birth weight of neonates in the two NICUs under study. The mean gestational age and the mean birth weight in the neonates of both NICUs were not significantly different. In a study,[22] the mortality rate was higher in small NICUs (less than 36 VLBW admissions per year) than in larger units; in this study although the rate of admission was higher in Shahid Beheshti hospital, but both NICUs are large and are the only two referral NICUs of the province. One of the probable causes of higher neonatal mortality in Alzahra NICU could be the higher rate of referred neonates to this hospital than in the other hospital, most of the hospitalized neonates were those born in this hospital and nursery personnel in this NICU had more experience.

In conclusion, our study showed that even with modern perinatal technology and care, early deaths of VLBW infants are common in our hospitals. The outcome of infants born at 24-28 weeks was unfavorable, but the prognosis improved rapidly with increasing maturity. Given that it is suggested that two thirds of all first-week deaths can be prevented by simple practices[30-32] and that improvement in health care professional skills would reduce the mortality and morbidity of neonates. The difference in mortality of the two hospitals confirms that mortality and morbidity rates should be continuously followed up and that differences should be evaluated in perinatal audit procedures.

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Ethical approval: The procedures followed were in accordance with the ethical standards of the Ethical Committee of Isfahan University of Medical Sciences (IUMS) and with *the Helsinki Declaration* of 1964, as revised in 2000. The study was approved by the IUMS Ethical Committee, and informed consent was obtained from the parents of all hospitalized neonates.

Competing interest: None to declare.

Contributors: Navaei F proposed the study and wrote the first draft, Kelishadi R contributed in conducting the study. All authors contributed to the design and interpretation of the study and to further drafts.

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