RESEARCH BRIEF

Survival and Morbidity Among Two Cohorts of Extremely Low Birth Weight Neonates from a Tertiary Hospital in Northern India

KANYA MUKHOPADHYAY, DEEPAK LOUIS, SRINIVAS MURKI, RAMA MAHAJAN, *MR DOGRA AND PRAVEEN KUMAR

*From the Neonatal Unit, Department of Pediatrics; and *Department of Ophthalmology; Postgraduate Institute of Medical Education and Research, Chandigarh, India.*

Correspondence to:
Dr Kanya Mukhopadhyay,
Additional Professor,
Department of Pediatrics, PGIMER,
Chandigarh 160 012, India.
kanyapupul@yahoo.com
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This study was conducted to compare the survival and morbidity of extremely low birth weight neonates born during two different time periods (2009-10 and 2001-02) at a Level III referral neonatal unit in Northern India. All consecutive intramural extremely low birth weight neonates (<1000g), irrespective of gestation, and admitted to Intensive Care were enrolled. 149 and 123 neonates were enrolled during 2009-10 and 2001-02, respectively. The baseline characteristics were comparable except for mean birth weight, which was lower during 2009-10 (843±108g *vs* 885±126g, *P*=0.003). Surfactant therapy (54% *vs* 18%, *P*<0.001), non-invasive ventilation (28% *vs* 6%, *P*<0.001), high frequency ventilation (24% *vs* 4%, *P*=0.001), IVH (52% *vs* 25%, *P*<0.001) and PDA (34% *vs* 18%, *P*=0.004) were significantly more during 2009-10. Culture positive sepsis (33% *vs* 51%, *P*=0.003) and ROP rates (7% *vs* 23%, *P*=0.042) were significantly higher during 2001-02. Overall survival was similar; however, neonates between 28-30 weeks gestation had better survival (63%) during 2009-10 compared to 2001-02 (38%), *P*=0.009. Survival in neonates 28-30 weeks improved during this period while overall survival remained the same.

Keywords: *Comparison, ELBW neonate, India, Morbidity, Outcome, Survival.*

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Extremely low birth weight (ELBW) neonates (<1000g at birth) form a very special high risk cohort among neonates, and are the most vulnerable for developing varied morbidities. Data on survival and morbidity of ELBW neonates are mostly from developed countries. It suggests a significant decline in mortality among ELBW neonates between 1990-91 and 1995-96 [1]. They also found that incidence of major disorders including necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD) increased from 1990-91 to 1995-96 while it remained static between 1995-96 and 1997-2002.

Similar information is lacking from developing countries [2,3]. However, there is no data showing trends in mortality or the incidence of morbidities among ELBW neonates from our country. Thus, we compared the survival and morbidity among ELBW neonates born in our centre during 2009-10 and 2001-02.

METHODS

This study was conducted in a level III referral neonatal unit of a teaching hospital in Northern India. All intramural ELBW neonates born during two separate time-periods, *i.e.* 2009-2010 and 2001-02 and admitted to neonatal intensive care were enrolled. Those with major/life threatening malformations were excluded. Extramural neonates were not included. Gestational age was based on maternal last menstrual period, and when available, ultrasound based assessment was used and confirmed postnatally by New Ballard Score [4]. Small for gestational age (SGA) was defined when birth weight was <10th centile as per Lubchenco's intrauterine growth charts [5]. Morbidities affecting these neonates and their mortality during hospital stay were recorded. These neonates were followed till death or discharge from the hospital. Informed consent was obtained from parents and the Institute Ethics Committee approved the study.

After initial stabilization in the delivery room, these neonates were shifted to intensive care unit with consent of parents who were willing for care. Neonates with respiratory distress syndrome were managed with early rescue surfactant and early continuous positive airway pressure (CPAP) during 2009-10, while its use was less during 2001-02 due to non-availability of surfactant. Those who failed CPAP were given a trial of nasal intermittent positive pressure ventilation (NIPPV) during the period 2009-10 before initiating mechanical ventilation. High frequency ventilation was used as a rescue mode during both time periods. Trophic feeding

was initiated at the earliest and transitioned gradually to full feeds depending on their tolerance, which was similar during both time periods. Blood culture by BACTEC method was used for bacterial isolation in neonates during 2009-10 while conventional blood cultures were used during 2001-02 period. Echocardiography was used for identification of hemodynamically significant patent ductus arteriosus (PDA) in symptomatic babies. Screening head ultrasonogram (USG) was done once before day 4 of life, on day 7-14 of life and prior to discharge or at 36 to 40 weeks postmenstrual age (PMA) in asymptomatic babies by a trained neonatologist. Retinopathy of prematurity (ROP) screening was done at 28 days postnatal age by trained ophthalmologists and laser therapy provided, when indicated.

Standard definitions were used for defining various morbidities during both time periods. BPD was defined based on the criteria of receiving oxygen therapy of >21% for ≥28 days [6]. IVH was graded using Volpe's classification [7]. NEC was defined as per modified Bell's staging [8]. ROP was classified using International Classification of Retinopathy of Prematurity (ICROP) classification [9].

Statistical analysis: Descriptive statistics was used for describing baseline variables. Chi-square test was used for categorical variables and independent t test or Mann Whitney U test was used for continuous variables depending on their distribution. A *P* value of <0.05 was considered significant.

RESULTS

During 2009-10, 149 of 255 ELBW neonates and during 2001-02, 123 of 181 ELBW neonates were shifted to NICU and enrolled (***Table* I**). The remaining neonates were not shifted due to either non-availability of beds, parents unwilling for care or death in labor room. Birth weight was significantly lower in neonates born during 2009-10 compared to 2001-02 while gestational age was similar. Antenatal steroids was received by 111 (75%) mothers during 2009-10, while this data was not available for 2001-02.

Comparison of morbidity is depicted in ***Table* II**. Surfactant therapy, ventilation including noninvasive ventilation and high frequency ventilation, PDA, IVH including grade 3 or 4 IVH were significantly more common during 2009-10 while culture positive sepsis and ROP were more during 2001-02.

Seventy-eight neonates (52%) survived during 2009-10 period while 56 (46%) survived during 2001-02. Their survival comparison is depicted in ***Table* III**. None of the neonates <500g during either time periods survived. Overall survival rate was similar in 2 periods but survival at 28-30 weeks gestation improved significantly (*P*=0.009) from 38% in 2001-2 to 63% in 2009-10.

TABLE I BASELINE CHARACTERISTICS OF ELBW NEONATES

	2009-10 (n=149)	*2001-02 (n=123)*
Gestational age (wks)	29.1 ± 2.6	29.5 ± 2.6
Birthweight*	843 ± 108	885 ± 126
Males	78 (52)	66 (54)
SGA	77 (52)	57 (46)
LSCS	48 (32)	32 (26)
Maternal medical illness*	33 (22)	14 (11)
Obstetric complications*	127 (85)	91 (74)
Apgar at 1 min*#	6 (3,7)	6 (5,7)
Apgar at 5 min*#	8 (6,9)	8 (7,8)

*Values represent mean ± SD and n (%); #represent median [IQR]. SGA – small for gestational age; LSCS – lower segment caesarean section; *P<0.05.*

TABLE II MORBIDITY IN ELBW NEONATES DURING THE TWO PERIODS UNDER STUDY

	2009-10 (*n*=149)	2001-02 (*n*=123)	*P* value
Respiratory distress at birth	104 (70)	92 (75)	0.43
RDS	48 (46)	58 (63)	
Congenital pneumonia	26 (25)	14 (15)	
TTNB	30 (29)	20 (22)	
Surfactant therapy	56 (54)	23 (25)	<0.001
Any ventilation during hospital stay	99 (92)	66 (72)	0.02
Only non invasive ventilation	29 (28)	7 (8)	<0.001
High frequency ventilation	25 (24)	5 (5)	0.001
Mechanical ventilation	67 (64)	59 (64)	0.79
NEC	23(15)	25 (20)	0.69
NEC stage II or greater	15 (10)	17 (14)	0.25
PDA	51 (34)	23 (18)	0.004
Culture positive sepsis	49 (33)	63 (51)	0.003
IVH any grade	78 (52)	32 (25)	<0.001
IVH grade 3 or 4	39 (26)	14 (11)	0.002
BPD	19 (13)	9 (7)	0.14
ROP	10 (7)	28 (23)	0.042
ROP requiring laser therapy	2 (1.3)	10 (8)	0.85

Values represent n (%). NEC-necrotizing enterocolitis, PDA-patent ductus arteriosus, IVH- intraventricular hemorrhage, BPD-bronchopulmonary dysplasia, ROP-retinopathy of prematurity.

TABLE III SURVIVAL BASED ON GESTATIONAL AGE AND BIRTH WEIGHT DURING BOTH TIME PERIODS

	Unadjusted survival			*Adjusted survival**		
	2009-10 (n=255)	*2001-02 (n=181)*	*P value (n=149)*	*2009-10 (n=123)*	*2001-02*	*P value*
<28 weeks	9/108 (8)	10/61 (16)	0.18	9/42 (21)	10/31 (32)	0.29
28-30 weeks	39/95 (41)	19/70 (27)	0.09	39/62 (63)	19/50 (38)	0.009
>30 weeks	30/52 (58)	27/50 (54)	0.86	30/45 (67)	27/42 (64)	0.82
<500g	0/3 (0)	0/1 (0)	–	0/3 (0)	0/1 (0)	–
500-750g	7/69 (10)	7/48 (15)	0.66	7/22 (32)	7/21 (33)	0.92
>750g	71/183 (39)	49/132 (37)	0.86	71/124 (57)	49/101 (48)	0.19

*Values are n (%). A P value <0.05 is significant. *Adjusted included only those neonates who got transferred to intensive care.*

DISCUSSION

The survival in 28-30 weeks gestation improved significantly in 2009-10 probably due to surfactant therapy, and non-invasive and high frequency ventilation. Surfactant was introduced only in the early 2000 to India and this could explain its reduced use in neonates born during 2001-02 compared to the later period. The benefits of early surfactant have been clearly shown by numerous randomized controlled trials and in a recent Cochrane review [10]. The same reason explains the use of non-invasive ventilation, especially CPAP, which has become a standard of care among pre-term neonates with respiratory distress syndrome. The evidence for this comes from trials that showed that a significant proportion of these neonates, including the extremely low birth weight neonates, could be managed with CPAP alone, without needing mechanical ventilation [11,12].

IVH occurred more frequently in the 2009-10 than 2001-02. IVH is multi-factorial in etiology and in our study population, at least two of these risk factors namely PDA and mechanical ventilation [13] were more prevalent in the 2009-10 cohort, and there were more number of survivors in 28-30 weeks gestation who are more likely to develop IVH. It might also be due to our increasing expertise with neonatal imaging, especially head ultrasound and echocardiography, that we were able to pick up more IVH and PDA during the latter period. The decline in culture positive sepsis could be due to improvements in hand hygiene and better aseptic precautions during procedures. This also could be due to increased pre-treatment of mothers with antibiotics, especially when presenting with preterm rupture of membranes in the setting of preterm labor. Further, this occurred despite the fact that we were using BACTEC cultures for bacterial isolation during the latter period, which has higher rates of bacterial isolation than the conventional cultures [13]. Lower rates of ROP could be due to more rigorous monitoring of saturation as we became more aware of the harmful effects of oxygen in the pathogenesis of various diseases including BPD and ROP [14,15].

Better survival for neonates born between 28-30 weeks during 2009-10 could be due to the advances in perinatal and neonatal care that occurred between the two time periods, including antenatal steroids, surfactant therapy and noninvasive ventilation. However, such improvements were not reflected in those born <28 weeks or >30 weeks and the reason for this is probably that we need to improve care in the <28 weeks group and the existing care is optimal at >30 weeks of gestation though we should try to improve further. Our birth weight-wise survival analysis did not find any significant difference between the two periods. Fanaroff, *et al*. [1] from the NICHD network found that in neonates weighing 501-750 g, mortality decreased from 59% in 1991-92 to 46% in 1995-96 and stayed at 45% for 1997-2002. For the 751-1000 category, it declined from 19% to 14% during

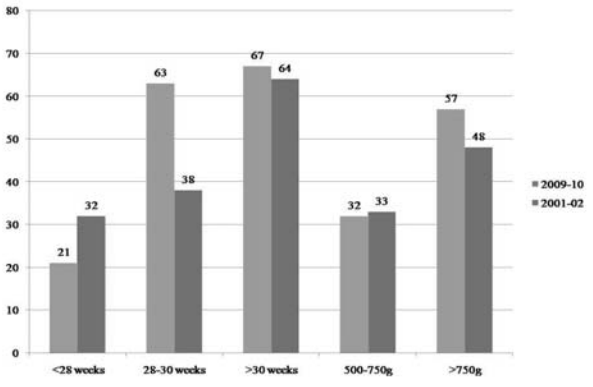

FIG. 1 *Adjusted survival based on gestation and birth weight categories during both time periods (values represent %).*

WHAT THIS STUDY ADDS?

- The Survival was found to be improving in the last decade amongst ELBW neonates, especially in 28-30 weeks gestation group,

1991-92 to 1995-96 and it reached 12% during 1997-2002. In a Swedish national prospective study conducted during the years 1990-1992, the average neonatal mortality among ELBW cohort was 37%, but their gestational ages were much lower compared to our cohort [16]. Another retrospective study in 1998 from Taiwan showed an overall neonatal survival of ELBW neonates to be 74% and survival to discharge of 60% [17]. Survival was 40% for neonates <750g and 68% for those >750g. Their survival in babies <26 weeks gestation was 27% while those above 26 weeks, it was 72%.

The shortcomings of our study were that we did not use an objective score to assess the severity of neonatal illness, which could have improved the comparability between the two cohorts; and did not systematically look at the practices that would have changed the outcome in these neonates during these two time periods. We were also not able to look at the effect of antenatal steroids as we did not have data for the same in the former cohort. Optimum care could not be provided to all ELBW neonates due to financial constraints and non-availability of beds. The strengths are that we had adequate number of babies who were enrolled and no previous study from India has made such a comparison between two time periods over a period of 10 years.

In conclusion, though the survival is increasing in our set-up, it is far below than that off from developed countries.

Contributions: KM: conceptualized the study, supervised data collection and reviewed the manuscript; DL: Analyzed data and prepared the manuscript; SM: Collected the data of 1st cohort; RM: Collected the data of 2nd cohort; MR: Provided data on ROP; and PK: Critically reviewed the manuscript.
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