Evaluation of Perinatal and Management Factors Associated with Improved Survival in Extremely Low Birth Weight Infants

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Purpose : The aim of this study was to evaluate recent improvements in the survival rate of extremely low birth weight (ELBW) infants and to identify perinatal and management factors that are associated with improved survival.

Methods : Two groups of ELBW infants who were admitted to our neonatal intensive care unit (NICU) during two distinct eras : November 1994–December 1999 (Period 1 : n=100) and January 2000–April 2004 (Period 2 : n=166) were retrospectively reviewed.

Results : Despite the younger gestational age and smaller birth weight of the ELBW infants in period 2, not only did their survival rate increased to 75 percent from 60 percent in period 1, but their incidence of morbidities such as bronchopulmonary dysplasia, confimed sepsis and intraventricular hemorrhage (≥Grade III) also declined. Factors significantly associated with improved survival included the use of antenatal steroids, a longer duration of nasal continuous positive airway pressure and the absence of intraventricular hemorrhage (≥Grade III).

Conclusion : We believe that optimized clinical practice, that emphasized less invasive care, contributed to the recent improvements in the survival rate of ELBW infants. **(Korean J Pediatr 2005;48: 1324–1329)**

Key Words : Extremely low birth weight, Survival, Morbidity, Prematurity

Introduction

Remarkable progress in prenatal and neonatal care during recent decades has led to a dramatic improvement in the survival of preterm infants. By the early 1990s, the introduction of surfactant therapy had resulted in an increased likelihood of survival of smaller preterm infants, especially those of very low birth weight (VLBW) infants under 1,500 g and extremely low birth weight (ELBW) infants under 1,000 g. In developed countries, almost all neonatal intensive care units had survival rates of >90%

for infants with birth weights >1,000 g[1, 2]. Consequently over the past decade, more efforts have been concentrated on improving the survival and care of ELBW infants. In western cohort studies, such as those conducted in the late 1990s by the Vermont Oxford Network Group, the University of Chicago (USA) and the Victorian Infant Collaborative Study Group (Australia), survival rates reached more than 70%[1, 3, 4], while Japanese studies showed survival rates of more than 80% during the same period[5, 6]. The survival and morbidity rates of ELBW infants are also reliable indicators of the quality of NICU care, so it is crucial to obtain accurate survival data. Recent Korean studies, however, mostly focused on increase in survival rate during the late 1990s, and articles with a study period including the era after 2000 are rare[7-10]. Thus, the aim of this study was to evaluate whether the survival rate of ELBW

infants in our NICU had increased in the era since 2000, given recent improvements in the quality of NICU care, and to determine the factors associated with improved survival and quality of care for those micropremies.

Materials and Methods

The subjects comprised 266 liveborn infants weighing less than 1,000 g at birth who were consecutively admitted to Samsung Medical Center during two distinct eras : November 1994-December 1999 (period 1, n=100) and January 2000-April 2004 (period 2, n=166). Survival in our study was defined as being alive at the time of discharge from NICU. Survival rates between the two periods were compared and then further analyzed according to birth weight (BW) and gestational age (GA). Clinical data collected from the medical records, such as maternal and neonatal characteristics regarding morbidities, perinatal factors and treatment, were also compared between the two periods after adjustment were made for BW and GA. Major morbidities included respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP). BPD was defined as an oxygenation dependency at 36 weeks' postmenstrual age compatible with radiologic finding, and IVH and ROP were limited to high grade illnesses ($\geq$Gr. III, requiring laser therapy, respectively). Perinatal and demographic characteristics included BW, GA, pregnancy induced hypertension (PIH), premature rupture of membrane (PROM), antenatal steroids and antibiotics therapy, chorioamnionitis, caesarian section delivery, and Apgar score.

Management factors included surfactant therapy, the duration of assisted ventilation, the use of dexamethasone and inotropics, PDA ligation, the duration of total parenteral nutrition (TPN) and enteral feeding, and the antibiotics therapy within the first week of life. Those clinical factors that showed a statistically significant difference between the two eras were then evaluated to assess their association with improved survival.

Statistical analysis was performed using univariate analysis for a comparison of clinical characteristics between the two eras. Clinical characteristics showing a significant difference were further analyzed by multivariate logistic regression to find their association with improved survival.

Statistical significance was accepted at the $P<0.05$ level.

Results

1. Survival rate

The overall survival rate of ELBW infants increased significantly, from 60% in period 1 to 75% in period 2 (Table 1). The BW specific survival rate shows that none of the neonates <500 g at birth survived in period 1, while 3 (43 %) of 7 infants <500 g at birth and 5 (42%) of 12 infants between 500 to 599 g survived in period 2. Moreover, the minimun BW achieving a survival rate of more than 50% in period 2 was 600-699 g, much lighter than 800-899 g in period 1. A similar pattern was noted in GA specific survival rate. None of the infants at 24 week of GA survived in period 1, while 15 (54%) of 28 infants survived in period 2. The minimum GA achieving a survival rate of more than 50% in period 2 was 24 week, much younger than 26 week in period 1. The most impressive improvement in survival rate over the eras was observed in the GA range of 24-25 week with a survival increase of more than 50%.

2. Major morbidities

Table 2 shows a comparison of major morbidities between the two periods after adjusting for BW and GA. The incidence of RDS did not differ significantly between the periods, but the incidence of BPD was significantly decreased in period 2 (34% vs 16%). Incidence of PDA, NEC,

Table 1. Survival Rate of ELBW Infants by Birth Weight and Gestational Age

	Period I (94-99)	Period II (00-04)
Birth weight (g)		
<500	0/0 (0%)	3/7 (43%)
500-599	1/5 (20%)	5/12 (42%)
600-699	5/12 (42%)	12/20 (60%)
700-799	4/13 (31%)	29/35 (83%)
800-899	18/29 (62%)	34/47 (72%)
900-1,000	32/41 (78%)	41/45 (91%)
Gestational age (wk)		
<24+0	1/3 (33%)	2/9 (22%)
24+0-24+6	1/6 (17%)	15/28 (54%)
25+0-25+6	5/15 (33%)	24/30 (80%)
26+0-26+6	13/20 (65%)	28/35 (80%)
27+0-27+6	14/21 (67%)	21/24 (87%)
28+0-28+6	12/14 (86%)	12/14 (86%)
29+0-29+6	9/13 (69%)	11/13 (85%)
$\geq$30+0	5/8 (63%)	11/13 (85%)
Total	60/100 (60%)	124/166 (75%)

Table 2. Morbidities

	Period I (100)	Period II (166)	P
RDS[*] (%)	76 (76)	142 (86)	NS
BPD[†] (%)	34 (34)	26 (16)	0.001
PDA[‡] (%)	76 (76)	139 (84)	NS
NEC[§] (≥stage 2) (%)	2 (2)	7 (4)	NS
Confirmed sepsis (%)	54 (54)	50 (30)	<0.001
IVH[∥] (≥grade 3) (%)	15 (15)	15 (9)	0.031
PVL[¶] (%)	6 (6)	3 (2)	0.070
ROP[**] (LASER) (%)	19 (19)	30 (18)	NS

[*]RDS : respiratory distress syndrome, [†]BPD : bronchopulmonary dysplasia, [‡]PDA : patent ductus arteriosus, [§]NEC : necrotizing enterocolitis, [∥]IVH : intraventricularhemorrhage, [¶]PVL : periventricular leukomalacia, [**]ROP : retinopathy of prematurity

and ROP did not change significantly over the periods. However, the incidence of culture proven confirmed sepsis and IVH (≥grade 3) declined significantly in period 2 (54% vs 30%, 15% vs 9%).

3. Perinatal and demographic characteristics

As shown in Table 3, the mean BW and GA in period 2 were 794±143 g and 26±2 week respectively, and they were significantly decreased from 841±121 g and 27±2 week in period 1. The incidence of small for gestational age (SGA) infants did not differ significantly between the two periods (22% vs 26%). After adjusting for BW and GA, perinatal factors that showed a significant difference between the two periods were as follows : ELBW infants in period 2 were more likely to have received antenatal steroids (43% vs 61%), to have mothers with biopy proven chorioamnionitis (19% vs 36%), and to have higher 5-minute Apgar score (5±2 vs 6±2). However, the other perinatal factors such as the incidences of PIH, PROM and cesarean section, the use of antenatal antibiotics, and 1-minute Agpar score did not differ significantly between the two periods.

4. Management characteristics

In Table 4, management factors were compared between the two periods, after adjusting for BW and GA. Surfactant therapy was used more often in the later period (65% vs 84%). The duration of conventional ventilation (SIMV) was significantly shorter in period 2 (27±35 vs 19±31 days), but the durations of HFOV and nasal continuous positive airway pressure (n-CPAP) were significantly longer (3±6 vs 7±13 days, 6±11 vs 11±14 days, respectively) in the same period. On the other hand, the use of NO

Table 3. Demographic and Perinatal Characteristics

	Period I (100)	Period II (166)	P
Birth weight (g)	841±121	794±143	0.006
Gestational age (wk)	27±2	26±2	0.015
SGA[*] (%)	22 (22)	43 (26)	NS
PIH[†] (%)	23 (23)	37 (22)	NS
PPROM[‡] (hr)	39±93	39±109	NS
Antenatal steroids (%)	43 (43)	97 (61)	0.007
Antenatal antibiotics (%)	39 (39)	79 (50)	NS
Chorioamnionitis (%)	19 (19)	53 (36)	0.011
Caesarian section (%)	60 (60)	114 (69)	NS
Apgar score at 1 min	3±2	3±2	NS
Apgar score at 5 min	5±2	6±2	0.004

[*]SGA : small for gestational age, [†]PIH : pregnancy induced hypertension, [‡]PPROM : preterm premature rupture of membrane

Table 4. Management Factors

	Period I (n=100)	Period II (n=166)	P
Surfactant use (%)	65 (65)	139 (84)	0.006
SIMV[*] (day)	27±35	19±31	0.028
HFOV[†] (day)	3±6	7±13	0.043
NO[‡] (%)	8±8	12±7	NS
NCPAP[§] (day)	6±11	11±14	0.001
Dexamethasone use (%)	50 (50)	63 (38)	0.020
Antibiotics within 1 wk (%)	95 (95)	124 (75)	0.001
Inotropics use (%)	68 (68)	88 (53)	0.001
PDA[∥] ligation (%)	19 (19)	21 (13)	NS
Enteral feeding start (day)	9±6	6±5	0.002
Time to full feeding (day)	39±26	33±29	0.013
TPN[¶] duration (day)	27±26	25±10	NS

[*]SIMV : synchronized intermittent mandatory ventilation, [†]HFOV : high frequency oscillatory ventilation, [‡]NO : nitric oxide, [§]NCPAP : nasal continuous positive airway pressure, [∥]PDA : patent ductus arteriosus, [¶]TPN : total parenteral nutrition

gas did not show significant difference between the periods. Meanwhile, the use of antibiotics within the first week of life and the use of dexamethasone declined significantly in period 2 (95% vs 75%, 50% vs 38%, respectively). Inotropics were used significantly less often (68% vs 53%) in period 2, but the incidence of PDA ligation did not change significantly over the periods. The time to start enteral feeding and to achieve full enteral feeding both occurred significantly earlier in period 2 (9±6 vs 6±5 days, 39±26 vs 33±29 days, respectively). However, the duration of TPN was not significantly different between the periods.

Table 5. Logistic Regression Analysis of Factors Associated with Improved Survival

Variable	OR[‡]	95% CI[§]	P[‖]
Birth weight	0.996	0.993-0.998	<0.001
Gestational age	0.963	0.939-0.989	<0.001
Period 2	3.854	2.036-7.296	<0.001
Antenatal steroids (use)	2.25	1.23-4.11	0.008
Apgar score 5 min (1 point higher)	0.86	0.73-1.02	0.086
NCPAP[*] (10 days longer)	3.60	1.20-6.10	<0.001
Enteral feeding start (5 days faster)	1.66	1.49-1.97	0.065
Absence of IVH[†] (≥grade 3)	6.81	2.49-18.61	<0.001

[*]NCPAP : nasal continuous positive airway pressure, [†]IVH : intraventricular hemorrhage, [‡]OR : odds ratio, [§]CI : confidence interval, [‖]P was adjusted for birth weight & gestational age & period

5. Clinical factors associated with improved survival

After adjusting for BW, GA and era, logistic regression analysis was conducted using the above clinical factors that showed significant difference between the two periods. Factors significantly related to improved survival in period 2 were as follows : the use of antenatal steroids, a longer duration of n-CPAP ventilation and the absence of IVH (≥grade 3). The odds ratios (OR) with a 95% confidence interval (CI) of these factors are shown in Table 5.

Discussion

Survival of the ELBW infants has been a major concern for most of the NICUs worldwide over the past few decades because not only more ELBW infants now survive due to recent advances in prenatal as well as neonatal intensive care, but these surviving micropremies also must deal with the risk of major morbidities. In the studies of the ELBW infants published in Korea, Choi et al. reported a survival rate of 50% in 1998[8], and Kim et al. recently reported a survival rate of 65.7% during 1999-2002[9]. In our study, the survival of ELBW infants showed a remarkable improvement, achieving 75% which is comparable to that of Vermont Oxford and University of Chicago studies. This implies that Korean neonatal intensive care at least at this single center has reached the level seen in developed countries. The minimum BW and GA achieving a survival rate of more than 50% was significantly smaller and younger in period 2, showing that the survival rate in the later period

rose dramatically due to the greater survival of a subgroup of smaller and younger infants. Furthermore, morbidities such as BPD, confirmed sepsis and high grade IVH declined significantly in the later period, despite greater number of smaller and younger infants with their associated higher risk of serious complications. We believe that due to improved quality of NICU care, the younger and smaller ELBW infants in period 2 survived longer with less complications, ultimately contributing to a significantly improved overall survival rate in the later period.

Among the clinical factors responsible for improved quality of our NICU care, the two main factors were the availability of more effective perinatal care and the less invasive management. More frequent administration of antenatal steroids and higher 5-minute Apgar score in period 2 suggest vigorous resuscitation and perinatal care of the ELBW infants. Moreover, highly skilled fellow neonatologists participated in the teamwork of resuscitation in the delivery room, and the resident doctors and NICU nurses were educated and tested regularly regarding neonatal resuscitation.

In additon, our clinical practice emphasized less invasive care during the later period, which was reflected in significant difference in clinical characteristics between the two review periods. First, the duration of n-CPAP was significantly longer while the incidence of BPD declined significantly in period 2. This was accomplished by encouraging early extuabation with the application of n-CPAP to prevent barotrauma and chronic lung damage that result from mechanical ventilation. A shortcoming of this study is that we could not determine whether the longer duration of n-CPAP could be partly attributed to the longer survival of infants in period 2, thus providing more opportunities to apply n-CPAP. Therefore, prospective evaluation of ventilation management is needed to rule out the selection bias.

Secondly, enteral trophic feeding was started earlier in period 2. Similar to our recent study by Jeon et al.[11], a beneficial effect was demonstrated as the time to achieve full enteral feeding was shortened without an increase in complications, such as NEC and sepsis. Thirdly, the management policy for infection control had been changed. Infection control is crucial because infection is known to be a major cause of death in ELBW infants[12, 13]. Indwelling umbilical catheters were replaced by percutaneous central venous catheters (PCVC) as soon as possible in order to minimize catheter-related sepsis and vascular complications

[14]. The routine use of empirical antibiotics within the first few days following birth was also minimized to reduce the risk of nosocomical sepsis[15, 16]. During period 2, there was a decrease in the incidence of sepsis, despite the less frequent use of initial antibiotics. This shows that the judicious use of antibiotics when they are truly necessary actually helps to lower the incidence of sepsis. In addition to these strategies for less invasive care, fluid therapy for the ELBW infants was modified. The ambient humidity of the incubator was maintained near 100% during the first week after birth. This minimized insensible water loss so that moderate fluid restriction was possible, thus preventing fluid overload which has been reported[17, 18] to influence morbidities such as PDA, IVH and BPD.

As a result of active perinatal care and less invasive management, specific clinical factors associated with improved survival in period 2 were the use of antenatal steroids, a longer duration of n-CPAP and the absence of IVH (≥Grade III). High grade IVH is a frequent cause of death in case of extreme prematurity[9, 13]. The absence of high grade IVH showed the strongest association with improved survival. Our assumption is that the less invasive care may have caused less fluctuation in respiratory and cardiovascular homeostasis, thus reducing the risk of occurrence of high grade IVH. The drawback of this study is that long term follow up was not included. Most parents are very concerned about long term outcome for conditions which may influence quality of life, such as cerebral palsy, mental retardation, blindness, and hearing loss. These disabilities are becoming a major issue as more micropremies are surviving. Therefore, a prospective study with long term outcome is needed in the future in order to evaluate quality-adjusted survival.

In conclusion, our study demonstrated that less invasive management, along with active resuscitation and perinatal care, enhanced the quality of NICU care. This change in treatment has promoted the younger and lighter ELBW infants to survive with significant decrease in morbidities ultimately contributing to recent improvements in overall survival of ELBW infants.

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한 글 요 약

출생 체중 1,000 g 미만의 초극소 미숙아의 생존율 향상과 연관된 산과 및 치료인자

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목 적 : 최근 1,000 g 미만의 초극소 미숙아의 생존율이 괄목할 만큼 향상되었고 이는 또한 신생아 집중치료술 평가의 지표로 간주되고 있어 초극소 미숙아의 생존율이 얼마나 향상되었는지를 평가하고 생존율 향상과 연관된 주산기 및 치료인자를 알아보고자 하였다.

방 법 : 본원 신생아 중환자실에 입원한 출생 체중 1,000 g 미만의 초극소 미숙아들을 대상으로 1994년부터 1999년까지를 1기(n=100)로, 2000년부터 2004까지를 2기(n=166)로 분류하여 후향적 의무기록 분석을 통해 두 시기의 임상양상을 비교하였다.

결 과 : 1기에 비해 2기에서 평균 재태연령과 출생 체중(27±2주, 841±121 g vs. 26±2주, 794±143 g)이 유의하게 낮았으나 생존율이 60%에서 75%로 현저히 향상되었다. 또한 재태연령과 출생 체중을 보정한 분석에서 두 시기간 유의한 차이를 보인 합병증으로는 기관지폐이형성증, 균혈증이 확인된 패혈증과 3도 이상의 뇌실내 출혈로 2기에서 낮은 빈도를 보였다. 대상 환아들의 생존율 향상과 연관된 주산기 및 치료인자를 확인하기 위해 두 시기 간 유의한 차이를 보인 임상인자를 로짓회귀분석을 한 결과 산전 스테로이드 치료, 비강 지속성 기도 양압 치료기간과 3도 이상의 뇌실내 출혈의 부재가 포함되었다.

결 론 : 본원의 초극소 미숙아들의 생존율이 최근 향상된 것은 덜 침습적인 치료 방법을 중요시 여겼던 신생아 중환자실팀의 임상적 관리의 향상을 바탕으로 산전 스테로이드 치료 증가, 비강 지속성 양입기도 사용 증가와 3도 이상의 뇌실내 출혈감소에 기인한 것으로 사료된다.

References

1) Meadow W, Lee G, Lin K, Lantos J. Changes in Mortality for extremely low birth weight infants in the 1990s : implications for treatment decisions and resource use. Pediatrics 2004;113:1223-9.
2) Teberg AJ, Hodgman JE, Barton L, Chan LS. Nursery survival for infants of birth weight 500-1,500 grams during 1982-1995. J Perinatol 2001:97-106.
3) Vermont Oxford Network 2000-2001. Society for Pediatric Research Meeting May 2002 : mail@vtoxford.org.

4) Doyle LW. Evaluation of neonatal intensive care for extremely low birth weight infants in Victorea over two decades : I. Effectiveness. Pediatrics 2004;113:505-9.

5) Nishida H. Outcome of infants born preterm, with special emphasis on extremely low birth weight infants. Baillieres Clin Obstet Gynecol 1993;7:611-31.

6) Nishida H. Perinatal health care in Japan. J Perinatol 1997; 17:70-4.

7) Bae YM, Bae CW. The changes in the mortality rates of low birth weight infant and very low birth weight infant in Korea over the past 40 years. J Korean Med Sci 2004; 19:27-31.

8) Choi CW, Choi JW, Jo HS, Kim HS, Park JD, Kim BI, et al. Statistical study of extremely low birth weight infants. Korean J Perinatol 1998;9:3-11.

9) Kim JT, Park HK, Jun NL, Lim JW, Kim AR, Pi SY, et al. Recent outcome of extremely low birth weight infants at Asan Medical Center. J Korean Soc Neonatol 2003;10: 133-42.

10) Choi CW, Hwang JH, Shim JW, Kim SS, Chang YS, Park WS, et al. Change in the limit of viability of fetal infants. J Korean Pediatr Soc 2003;46:1194-99.

11) Jeon GW, Park SE, Choi CW, Hwang JH, Chang YS, Park WS. The effects of early enteral feeding in extremely low birth weight infants. Korean J Pediatr 2005;48:711-15.

12) Hodgman JE, Barton L, Pavlova Z, Fassett MJ. Infection as a cause of death in the extremely low birth weight infant. J Matern Fetal Neonate Med 2003;14:313-17.

13) Barton L, Hodgman JE, Pavlova Z. Causes of death in the extremely low birth weight infant. Pediatrics 1999;103:446-51.

14) Kim BL, Hwang JH, Kang CK, Sim JW, Chang YS, Park WS, et al. The changes of incidence of nosocomical sepsis, and risk fators in extremely low birth weight infants. J Korean Soc Neonatol 2002;9:12-20.

15) Kollef M. Appropriate empirical antibacterial therapy for nosocomical infection : getting it right the first time. Drugs 2003;63:2157-68.

16) Louis JM, Eherenberg HM, Collin MF, Mercer BM. Perinatal intervention and neonatal outcomes near the limit of viability. Am J Obstet Gynecol 2004;191:1398-402.

17) Shaffer SG, Bradt SK, Hall RT. Postnatal changes in total body water and extracellular volume in the preterm infant with respiratory distress syndrome. N Engl J Med 1980; 302:598-604.

18) Korhonen P, Tammela O, Koivisto AM, Laippala P, Ikonen S. Frequency and risk factors in bronchopulmonary dysplasia in a cohort of very low birth weight infants. Early Hum Dev 1999;54:245-58.