□원저 : 임상□

Improved survival rate with decreased neurodevelopmental disability in extreme immaturity

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Purpose : The aim of this study was to determine whether improved survival of extremely low birth weight infants (ELBWI) was associated with decreased neurodevelopmental disability later in life, and also to identify the factors influencing this disability.

Methods : ELBWI admitted to the neonatal intensive care unit of Samsung Medical Center, survived, and followed up until the corrected age of 18 months were enrolled. They were divided into two groups according to admission time: period I (1994-1999, n=36) and period II (2000-2004, n=98). Clinical data were collected retrospectively from the medical records.

Results : Survival rates increased from 60.0% to 74.7%, cerebral palsy rates decreased from 22.2% to 8.2% and catch-up growth rate increased from 25.0% to 51.0% during period I and II. Despite less gestational age and birth weight, ELBWI during period II had less periventricular leukomalacia (PVL), sepsis and bronchopulmonary dysplasia compared to period I. The highest risk factors for cerebral palsy were intraventricular hemorrhage (IVH) (≥Grade III), failure of catch-up growth and PVL.

Conclusion : In summary, improved viability was associated with decreased neurodevelopmental disability in ELBWI. Improved neonatal care with resultant decrease in PVL and IVH, and better nutritional support seem to be primarily responsible for this improved outcome. **(Korean J Pediatr 2007;50:1067-1071)**

Key Words : Cerebral palsy, Developmental disabilities, Infant, Premature

Introduction

Recently, survival rates of extremely low birth weight infants (ELBWI) with birth weight less than 1,000 g have improved dramatically due to technologic and therapeutic advances in perinatal and neonatal intensive care[1, 2]. However, as ELBWI are at higher risk for neurodevelopmental sequelae compared with more mature preterm infants, questions have arisen whether the improved viability has been accompanied by increased impairment rates, with worse quality of life for these tinest survivors. Wilson-Costello et al[3] reported that the improved survival rates of ELBWI were associated with increased long-term neurodevelopmental sequelae. However, the intact survival rates with normal cognitive function have also increased with improved viability[4, 5]. Therefore, whether recent improved survival observed in ELBWI has been accompanied by increased sequelae is still controversial, and further studies will be necessary to clarify this.

In our neonatal intensive care unit (NICU), we have experienced improved survival for ELBWI from 60% in the period I (1994-1999) to 75% in the period II (2000-2004)[6-8]; quality improvement practices including better assisted ventilation techniques[9], nosocomial infection control protocol[10] fluid/electrolyte management and nutrition[11] were

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responsible for the improved viability observed in the latter period. In the present study, we thus tried to determine the relationship between the improved viability and outcome in ELBWI by comparing the neurodevelopmental impairment rates until the corrected age of 18 months among the survivors during the two periods, and also to identify the factors that might influence the outcome in these tiny infants.

Materials and methods

ELBWI admitted to the NICU of Samsung Medical Center, survived, and followed up until the corrected age of 18 months were enrolled. The infants were divided into two groups according to the admission time: 36 patients during period I (November 1994 - December 1999) and 98 patients during period II (January 2000-July 2004).

Clinical data were collected and analyzed retrospectively from the medical records during admission and outpatient follow-up visits until the corrected age of 18 months.

As we already have reported improved survival rate of ELBWI from 60% during period I to 75% during period II[6-8] in our previous studies, impairment rates until the corrected age of 18 months during the two periods were assessed in the present study to determine the relationship between improved viability and outcome. The assessment of outcome included cerebral palsy, hearing loss, blindness and growth and developmental status[12]. Cerebral palsy was defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture[13]. Three groups were defined according to the severity of handicap as follows: group 1, children who could walk independently; group 2, children who could not walk but who could sit independently; group 3, children who could not sit independently (unable to maintain head and trunk control)[14]. Hearing loss was defined as bilateral impairment requiring hearing aids, and blindness was defined as <20/200 visual acuity.

To identify the factors influencing the outcome, various perinatal and postnatal variables were evaluated. The perinatal and birth variables included: gestational age, birth weight, sex, intrauterine growth retardation (IUGR), gestational diabetes mellitus, pregnancy induced hypertension (PIH), antenatal steroids therapy, premature rupture of membrane (PROM), chorioamnionitis, delivery type and Apgar score at 5 minute. Neonatal morbidities included respiratory distress syndrome (RDS)[15], patent ductus arteriosus (PDA), confirmed with echocardiography, sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP). Sepsis was diagnosed when there were clinical signs of systemic infection with a positive blood culture[16]. BPD was defined as an oxygen dependency at the corrected age of 36 weeks (postmenstrual plus postnatal age), and IVH and ROP were limited to a high grade (=Gr. III) and a high stage requiring laser therapy, respectively. Catch-up growth was defined as normal (10 percentile-90 percentile) height, weight and head circumference at the corrected age of 18 months.

1. Statistical Analyses

The results were presented as mean standard deviation. Differences between period I and period II were analyzed using the chi-square test or Fishers exact test for dichotomous outcome data, and the t-test or Mann-Whitney U test for continuous data. Data were also analyzed using multiple linear regression models to adjust for potential confounding variables. A P value<0.05 was considered statistically significant.

Results

1. Study Population

Among 100 and 166 ELBWI admitted, 60 (60.0%) and 124 (74.7%) survived to discharge, and 36 (60.0%) and 98 (79.0 %) were followed up to 18 months of corrected age during period I and II, respectively (Table 1). The survival rate and follow up rate at 18 months of corrected age during period II were significantly higher than those during period I.

2. Outcomes at the Corrected age of 18 Months

The incidence of cerebral palsy decreased significantly from 22.2% during period I to 8.2% during period II (Table 2). However, the type and severity of cerebral palsy were not significantly different during the two study periods. Catch-up growth up to 18 months of corrected age during

Table 1. Study Population

	Period I	Period II	Total	P
Admission	100	166	266	
Survived to discharge (%)	60 (60.0)	124 (74.7)	184 (69.2)	0.02
Follow-up at 18 months (%)	36 (60.0)	98 (79.0)	134 (72.8)	0.002

Table 2. Outcomes at the Corrected Age of 18 Months

	Period I (n=36)	Period II (n=98)	*P*
Cerebral palsy (%)	8 (22.2)	8 (8.2)	0.027
Type of cerebral palsy			
Spastic quadriplegia (%)	5 (62.5)	3 (37.5)	0.619
Spastic diplegia (%)	3 (37.5)	0 (0.0)	0.200
Others (%)	0 (0.0)	5 (62.5)	0.026
Severity of cerebral palsy			
Group 1 (%)	5 (62.5)	5 (62.5)	1.000
Group 2 (%)	3 (37.5)	3 (37.5)	1.000
Group 3 (%)	0 (0.0)	0 (0.0)	1.000
Hearing loss (%)	1 (2.8)	3 (3.1)	0.932
Blindness (%)	0 (0.0)	0 (0.0)	1.000
Catch-up growth (%)	9 (25.0)	50 (51.0)	0.009

Table 3. Comparison of Perinatal Variables between Period I and II

	Period I (n=36)	Period II (n=98)	*P*
Gestational age (week)	$27^{+2}\pm1^{+3}$	$26^{+0}\pm2^{+0}$	0.045
Birth weight (g)	881±93	811±139	0.006
Male (%)	19 (52.8)	59 (60.2)	0.554
IUGR (%)	6 (16.7)	29 (29.6)	0.183
Gestational diabetes mellitus (%)	0 (0.0)	5 (5.1)	0.327
PIH (%)	5 (14.9)	28 (28.6)	0.167
Antenatal steroid (%)	20 (55.6)	58 (59.2)	0.838
PROM (%)	13 (36.1)	21 (21.4)	0.117
Chorioamnionitis (%)	7 (19.4)	41 (41.8)	0.022
Cesarean section (%)	23 (63.9)	69 (70.4)	0.530
Apgar score at 1 min	4±2	3±2	0.157
Apgar score at 5 min	5±2	6±1	0.021

IUGR, intrauterine growth retardation; PIH, pregnancy induced hypertension; PROM, premature rupture of membrane

period II was also significantly increased compared to that during period I. The incidence of hearing loss was not significantly different, and no case with blindness was observed during the two periods.

3. Factors Influencing the Outcome

Birth weight and gestational age were significantly lower, and Apgar score at 5 min was significantly higher during period II compared to those during period I (Table 3). Other perinatal factors including sex, IUGR, gestational diabetes mellitus, PIH, antenatal steroids therapy and delivery type were not significantly different during the two study periods.

Although RDS was significantly higher, the incidence of BPD during period II was significantly lower when compared to period I (Table 4). The incidence of PVL and sepsis during period II were also significantly lower than those during period I. Other neonatal variables including PDA, IVH and ROP were not significantly different between the two study periods.

Table 4. Comparison of Postnatal Variables between Period I and II

	Period I (n=36)	Period II (n=98)	*P*
RDS (%)	24 (66.7)	84 (85.7)	0.013
PDA (%)	27 (75.0)	86 (87.8)	0.105
Sepsis (%)	23 (63.9)	33 (33.7)	0.002
IVH (%)	3 (8.3)	5 (5.1)	0.443
PVL (%)	4 (11.1)	0 (0.0)	0.001
BPD (%)	16 (44.4)	21 (21.4)	0.009
ROP (%)	9 (25.0)	28 (28.6)	0.828
BAEP abnormalities (%)	6 (16.7)	23 (23.5)	0.477

RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; BAEP, brainstem auditory evoked potentials

Table 5. Factors Associated with Cerebral Palsy

	Odds ratio	95% Confidence interval	*P*
IVH	20.212	1.287-317.410	0.032
Failure of catch-up growth	9.033	1.069-76.314	0.043
PVL	7.500	0.977-57.550	0.025
BPD	2.968	0.371-23.745	0.305
Dexamethasone	0.747	0.047-11.966	0.836
Gestational diabetes mellitus	1.683	0.176-16.090	0.648
Apgar score at 5 min	0.959	0.472-1.951	0.908
Gestational age	0.889	0.760-1.039	0.140
Ventilator day	1.021	0.979-1.065	0.335
Birth weight	0.999	0.985-1.013	0.855
IUGR	27.836	0.212-3659.253	0.181
PROM	5.464	0.483-61.826	0.170
Antenatal steroid	0.832	0.067-10.315	0.886
Chorioamnionitis	0.606	0.072-5.068	0.644
PIH	0.028	0.000-2.409	0.115

IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; IUGR, intrauterine growth retardation; PROM, premature rupture of membrane; PIH, pregnancy induced hypertension

In regression analyses of these variables, IVH, failure of catch-up growth and PVL were three factors identified to be significantly associated with the development of cerebral palsy (Table 5).

Discussion

The primary aim of this study was to clarify the much debated issue of whether increased survival among infants at

the limit of viability is associated with increased neurodevelopmental disability and other significant morbidities later in life[3-5, 17]. In the present study, improved survival rate of ELBWI during period II was associated with decreased incidence of cerebral palsy, and better catch-up growth at 18 months of corrected age compared to period I. Therefore, our data support the assumption that improved viability is associated with reduced neurodevelopmental impairments in ELBWI[4, 5, 17].

In the present study, although birth weight and gestational ages were significantly lower, and the incidence of RDS was higher, better survival rates and less complications including sepsis, BPD and PVL were observed in ELBWI during period II when compared to those during period I. These results indicate that quality improvement practices including better assisted ventilation techniques[9], nosocomial infection control protocol[10], fluid electrolyte management and nutrition[11] were responsible for the improved viability and better outcome observed during the latter period. The ELBWI were divided into two groups according to time. More frequent administration of antenatal steroids and higher Apgar score at 5 minute in ELBWI observed during period II suggest that better perinatal care and resuscitation techniques have also contributed to this improved survival and outcome.

Wilson-Costello et al[3] reported recently that the improved survival rates of infants with a birth weight less than 1,000 g in the 1990s occurred with increased neonatal morbidity rates such as the incidence of BPD, high grade IVH, and PVL for infants with birth weights of 750 to 999 g, but not for infants with birth weights of 500 to 749 g. They speculated that although active resuscitation was nearly universally used for the larger infants, selective resuscitation and support were offered only to the most vigorous infants who were <750 g, who thus represented a selected group. They also speculated that the increased survival rates for smaller, less mature infants, who have higher rates of sepsis, PVL, BPD and postnatal steroid use have been associated with poorer neurodevelopmental outcome. However, in this study, the number of patients admitted, survived and followed up until the 18 months of corrected age during period II was more than two fold greater than that during period I. Furthermore, the improved survival in the less mature infants observed during period II in the present study was also associated with lower rate of sepsis, PVL and BPD, and eventually with better neurodevelopmetnal outcome. Contradictory to the results of Wilson-Costello et al[3], our data thus indicate that not the patient selection bias but the true technologic and therapeutic advances in the care of ELBWI are responsible for the association of the improved viability and outcome.

Shankaran et al[13] reported that cerebral palsy was associated with grade III-IV IVH and PVL in ELBWI with gestational age≤24 weeks, birth weight≤750 g, and 1-minute Apgar score≤3. Among the in-hospital variables, lower gestational age and birth weight, male infants, BPD and severe IVH were reported by Hoekstra et al[18] as the risk factors related to neurodevelopmental disability. In the present study, severe IVH and PVL were the best predictors of later development of cerebral palsy. Taken together, these findings suggest that the presence or absence of the immediate complications such as severe IVH, BPD and PVL strongly correlates with the outcome, and therapeutic strategies that could reduce these immediate complications will likely yield the best chances to improve the outcome in ELBWI.

Latal-Hajnal et al[19] reported that postnatal catch-up growth was a favorable predictor for neurodevelopmental outcome. In the present study, the failure of postnatal catch-up growth was significantly associated with the development of cerebral palsy. These findings indicate that, besides the immediate complications such as IVH and PVL, better postnatal nutritional management is also very important in improving the outcome in ELBWI. However, as the infants with severe IVH and PVL who are at the highest risk for neurodevelopmental disability frequently suffer from feeding difficulty, there is a possibility that impaired postnatal growth might be a manifestation rather than cause of impairments. However, our data of more universal increase in catch-up growth observed during period II suggest that better nutritional support[11] is primarily responsible for this improved catch-up growth and thereby neurodevelopmental outcome.

In conclusion, improved viability was associated with decreased neurodevelopmental disability in ELBWI. Failure to achieve catch-up growth at the corrected age of 18 months, PVL and IVH (≥Gr. III) were the best predictors for the later development of cerebral palsy. Therefore, further therapeutic advances in neonatal intensive care medicine could improve both the survival rate and prognosis simultaneously in ELBWI.

한 글 요 약

초극소저출생체중아의 생존율 향상에 따른 장기 신경발달 장애의 감소

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목 적 : 초극소저출생체중아의 생존율 향상에 따라 장기 신경발달 장애가 감소했는지 여부와 이들의 장기 신경발달의 예후 인자에 대해 알아보고자 하였다.

방 법 : 1994년 11월부터 2004년 7월까지 삼성서울병원 신생아 중환자실에서 입원 치료 받은 초극소저출생체중아 중 교정나이 18개월에 외래에서 추적관찰이 가능하였던 134명을 대상으로 하였으며 외래 방문 시 진찰소견과 의무기록을 후향적으로 분석하였다. 대상 환아를 1994년 11월부터 1999년 12월까지인 제 I기와 2000년 1월부터 2004년 7월까지인 제 II기로 나누었으며 각각 36명과 98명이 해당되었다.

결 과 : 제 I기에 비하여 제 II기에 재태연령과 출생체중이 낮았지만 생존율은 향상되었으며(제 I기: 60.0%, 제 II기: 74.7%) 뇌성마비는 감소하였고(제 I기: 22.2%, 제 II기: 8.2%) 따라잡기 성장은 향상되었다(제 I기: 25.0%, 제 II기: 51.0%). 뇌실주위 백질연화증, 패혈증과 기관지폐 이형성증의 이환율은 제 II기에 감소하였다. 뇌성마비의 가장 큰 위험요인은 3도 이상의 고도 뇌실내출혈, 따라잡기 성장의 실패와 뇌실주위 백질연화증이었다.

결 론 : 초극소저출생체중아의 생존율 향상은 장기적인 예후의 향상과 관련되어 있으며 신생아 관리의 질향상과 관련된 뇌실주위 백질연화증의 감소, 고도 뇌실내출혈의 감소, 더 나은 영양공급이 장기적인 예후의 향상과 관련된 것으로 보인다.

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