HK J Paediatr (new series) 2007;**12**:78-85

Original Articles

Changes in Mortality, Morbidity and Early Neurodevelopmental Outcomes among Extremely-low-birth-weight (ELBW) Infants Born in the Early and Recent Post-Surfactant Era

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Abstract Advances in perinatal medicine and the introduction of surfactant replacement therapy (SRT) have significantly improved the outcomes for extremely-low-birth-weight (ELBW) infants (defined as birth weight less than or equal to 1000 gram). We studied a retrospective cohort of 234 ELBW babies born between 1993 and 2002 at a tertiary perinatal centre. The mean birth weight was 762±144 gram (mean±SD) with mean gestational age of 26.2±2.4 weeks (mean±SD). Changes in mortality, major morbidity and early neurodevelopment outcomes were compared by dividing them into 2 periods vis the early surfactant era (1993-1996) and the recent surfactant era (1997-2002). The major change in the recent surfactant era has been the adoption of early rescue therapy by natural surfactant for all babies requiring ventilator support. Improvement in survival till discharge (84.7% compared with 56.4%, *p<0.001*), higher prevalence in use of antenatal steroid (66.7% compared with 38.6%, *p<0.001*), fewer babies born with 1-minute Apgar Score ≤3 (29.0% compared with 48.1%, *p=0.002*), shorter duration of mechanical ventilation (16.7±18.2 days compared with 26.7±21.0 days, *p=0.001*), and reduction in prevalence of retinopathy of prematurity (16.2% compared with 29.0%, *p=0.049*) and severe intra-ventricular hemorrhage (13.6% compared with 30.0%, *p=0.002*) were noted among the babies in the recent surfactant era. These were not associated with any significant increase in prevalence of cerebral palsy, hearing and visual impairment and low General Developmental Quotient among 126 infants (75.4% of survivors) who attended our neurodevelopmental assessment with a mean corrected age of 19.0±2.2 months. Differences between the early and recent groups suggest that advances in perinatal and neonatal intensive care, in addition to early rescue surfactant therapy contribute to improved survival and neonatal outcomes of ELBW infants. Despite the increasing number of ELBW survivors, there was no increase in adverse early neurodevelopment outcomes.

Key words Extreme low birth weight (ELBW) infants; Morbidity; Neurodevelopment outcome; Prematurity; Surfactant; Survival

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Received July 27, 2006

Introduction

Advances in prenatal and neonatal care during the past two decades have contributed to the improved survival of extremely-low-birth-weight (ELBW) infants.[1,2] Improved socioeconomics, better provision of prenatal care, the use of antenatal steroid, surfactant replacement therapy, better nutritional support and ventilatory strategies have played significant roles in the overall improvement in the outcome of ELBW infants. Among these, the use of antenatal corticosteroids and surfactant therapy have been associated with significant reduction in mortality.[3,4] Nevertheless, a

significant proportion of survivors might exhibit varying degree of handicap and impaired long-term health outcomes.[5] Recent results from multi-centre cohort studies as well as the National Institute of Child Health and Human Development Neonatal Research Network from the United States showed no improvement in early childhood neurodevelopmental outcomes among ELBW infants in the post surfactant era despite their better survival.[6,7]

Our study objective is to analyse a cohort of ELBW babies born at a tertiary perinatal centre in Hong Kong (Queen Mary Hospital and Tsan Yuk Hospital, QMH/TYH) during 1993-2002 after the introduction of surfactant therapy, and compare the secular changes in survival, major morbidity and short-term neurodevelopment outcome by dividing them into the early surfactant (1993-1997) and recent surfactant (1997-2003) era. Over the two study periods, there was a gradual evolution of various management protocols and treatment modalities in the care of these extremely premature infants. The major change between the first and second period with respect to surfactant use was that during the early surfactant period, surfactant therapy was selectively given as a late rescue therapy to those babies with established diagnosis of moderate to severe RDS and both artificial (Exosurf) and natural (Survanta) surfactants were used. After 1997, a well-established protocol for liberal and early rescue surfactant replacement therapy for all babies with clinical diagnosis of RDS, regardless of the stage or severity, was in place and all babies were treated with natural surfactant (Survanta or bLES-bovine Lipid Extract Surfactant). A number of the babies in this cohort were enrolled at the time of birth into a randomised trial comparing Survanta vs bLES for treatment of RDS.[8] The division of the current cohort into two groups was made to facilitate the statistical evaluation of changes during early and the recent post-surfactant periods as well as to identify other key factors leading to changes in outcome.

Patients and Methods

The QMH/TYH neonatal unit is a 15-bed neonatal intensive care unit with an annual delivery rate ranging from 4,500 to 6,000. It is a tertiary perinatal referral center receiving in utero transfers of high-risk deliveries and is the teaching hospital of the University of Hong Kong. For surveillance and audit purposes, a registry was established in 1993 to prospectively collect perinatal and outcome data of all very low birth weight infants (defined as babies with birth weight less than 1500 gram). The study cohort was identified from this registry and detailed information was extracted and verified by cross-referencing with the medical records of mothers and their babies.

A total of 234 infants weighing less than or equal to 1000 g were delivered during the study period. All subjects were born in the delivery room or operation theatre in our hospital except two: one was born at home and the other in the Accident & Emergency Department before admission into our Neonatal Intensive Care Unit. Stillbirths or deaths in the labour room were excluded. ELBW infants born in other hospitals and transferred to our centre for further management were also excluded

Baseline characteristics including birth weight, maturity, sex, race, plurality of pregnancy, small-for-gestational age (SGA) (defined as birth weight less than tenth percentile for gestational age) and 1-minute Apgar score were recorded. Neonatal complications including respiratory distress syndrome (RDS) requiring the use of surfactant, intraventricular haemorrhage (IVH), patent ductus arteriosus (PDA), necrotising enterocolitis (NEC), sepsis, chronic lung disease (CLD) and home oxygen dependency were studied. Duration of mechanical ventilation and hospital stay were studied to reflect the intensity of resources used in managing these babies. The neonatal survival (survival beyond 28 days), survival upon hospital discharge and the neurodevelopmental outcome at 18-20 months corrected age were used as the major outcome measurements. It is our standard protocol that all ELBW infants would have a full developmental assessment performed at a corrected age of 18-20 months using the Griffiths Mental Developmental Scales to evaluate their short-term neurodevelopmental outcomes.

Statistical Analysis

SPSS 11.0 was used for statistical analyses. Chi-squared and Fisher's exact tests, when appropriate, were used for analysing categorical variables. Student's t-test was applied for comparing continuous variables. Log rank test was applied to compare 28-day survival between the two cohort groups. Statistical analysis as a function of study year was performed by using linear regression for continuous variables. $P<0.05$ was accepted as the cut-off value for statistical significance.

Results

Birth Characteristics

The perinatal and birth characteristics of the study cohorts in the 2 periods (1993-1996 and 1997-2002) are presented in Table 1. There was no difference in the gestational age, birth weight (BW), sex, race, proportion of small-for-gestational age (SGA) babies & multiple pregnancies between the 2 groups. However, the proportion of babies with Apgar score between 0 and 3 was significantly lower (48.1% vs 29.0%) in the later cohort (p=0.002). The proportion of mothers of ELBW babies receiving antenatal steroids (defined as completion of a course of steroids at least 24 hours before delivery) was significantly higher in the later cohort, increasing from 35.5% to 66.1% (p<0.001).

Survival

A 28 days-survival analysis (Kaplan-Meier curve) was performed for the two groups (Figure 1). There was a significant improvement in survival in the recent group. The log-rank test yielded a p-value of <0.001. There was a steady improvement in survival-to-discharge across the study period at an average of 4.7% per year (p<0.001). Survival rate was over 90% at the end of the study period (Figure 2).

Two major factors, higher BW as well as more recent year of birth were significantly associated with improved survival (p<0.001 for both). When we categorised the survival according to birth weight (Table 2), the improvement was most significant in the 501-750 g (p=0.003) and 751-1000 g birth weight groups (p<0.001) in the 2 study periods. Similar significant improvement was demonstrated in the survival of ELBW babies born at 24-27 weeks (p=0.001) and 28-32 weeks (p=0.018) (Table 3). The majority of babies fell into these two groups (90% of total population).

Neonatal Morbidity

Table 4 shows the comparison of neonatal morbidity of ELBW infants between the two cohorts. The proportion of babies who had RDS requiring surfactant replacement based on clinical or radiological features was similar in both groups (65%). There was no difference in the incidence of

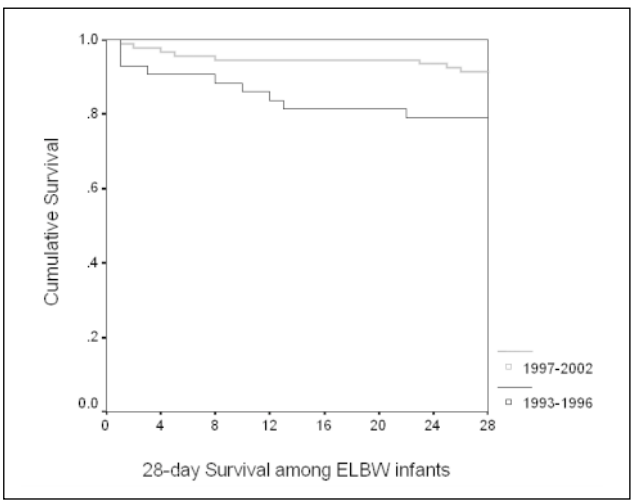

Figure 1 28-day survival curves of ELBW infants.

Table 1 Comparisons of birth characteristics between the cohorts in the 2 study periods

	1993-1996	**1997-2002**	***p*-value**
No. of live births	**110**	**124**	
Birth weight (grams)			
Mean±SD	762±144	793±143	0.104
Range	460-1000	450-995	
Gestational age (weeks)			
Mean±SD	26.2±2.4	26.7±2.2	0.100
Range	22-35	22-35	
Sex (M:F)	59:51	63:61	0.665
Ethnic Chinese	87 (79.1%)	95 (76.6%)	0.649
Multiple pregnancy	34 (30.9%)	37 (29.8%)	0.859
SGA*	46 (41.8%)	52 (41.9%)	0.986
Use of antenatal steroid	39 (35.5%)	82 (66.1%)	*<0.001*
1 minute Apgar score ≤3	53 (48.1%)	36 (29.0%)	*0.002*

Using either Student's t-test or χ^2-test, as appropriate

*SGA – Small for gestational age (Birth weight <10th percentile)

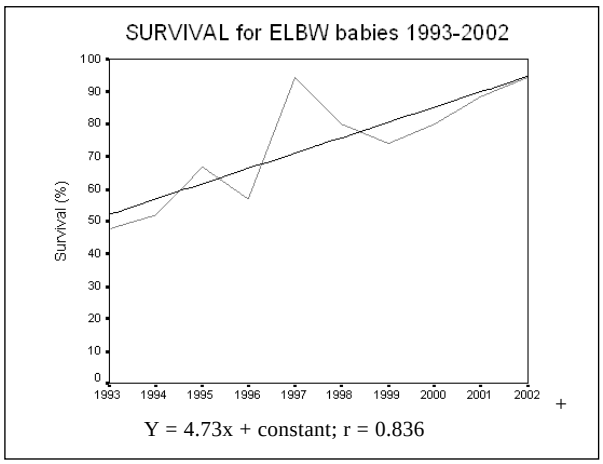

Figure 2 Survival figures of ELBW infants 1993-2002.

patent ductus arteriosus (54.8% vs 37.1%, p=0.074), of which 8% required surgical ligation. There was a significant decrease in the incidence of significant retinopathy of prematurity (ROP), defined as presence of stage III or above changes (International Classification of ROP), between the two groups. It decreased from 29.0% in the early cohort to 16.2% in the late cohort (p=0.049).

The number of reported cases of early-onset sepsis, defined as a positive blood culture within the first seven days of life, remained fairly constant. There was a decrease in the incidence of early blood stream infection from 6.4% to 3.2%. This was not statistically significant as the absolute number of cases (total=11) was small.

There was also a decreasing trend in reported cases of

Table 2 Survival rates of ELBW infants according to birth weight

Birth weight (grams)	**Survival on discharge (%)**				***p*-value**
	1993-1996		**1997-2002**		
500 g or below	2/4	(50%)	2/4	(50%)	1.000
501-750 g	18/47	(38.3%)	28/40	(70.0%)	*0.003*
751-1000 g	42/59	(71.2%)	75/80	(93.8%)	*<0.001*
Overall	62/110	(56.4%)	105/124	(84.7%)	*<0.001*

Table 3 Survival rates of ELBW infants according to gestational age

Gestational age (weeks)	**Survival on discharge (% of the cohort)**				***p*-value**
	1993-1996		**1997-2002**		
Below 24	0	(0%)	2/6	(33.3%)	*0.041*
24-27	44/75	(58.7%)	68/82	(82.9%)	*0.001*
28-32	16/21	(76.2%)	32/33	(97.0%)	*0.018*
33 or above	2/3	(66.7%)	3/3	(100%)	0.273
Overall	62/110	(56.4%)	105/124	(84.7%)	*<0.001*

Table 4 Comparison of neonatal morbidity of the cohorts in the 2 study periods

Morbidity	**1993-1996**	**1997-2002**	***p*-value**
SRT for RDS	74/110 (67.3%)	81/124 (65.3%)	0.753
Chronic lung disease	30/62 (50.8%)	60/105 (57.1%)	0.437
Home oxygen dependency	4/62 (6.9%)	11/105 (10.6%)	0.438
Patent ductus arteriosus			
Medical treatment alone	34/62 (54.8%)	39/105 (37.1%)	0.074
Surgical ligation	5/62 (8.1%)	9/105 (8.6%)	
Retinopathy of prematurity	18/62 (29.0%)	17/105 (16.2%)	*0.049*
Early-onset sepsis	7/110 (6.4%)	4/124 (3.2%)	0.258
Severe IVH (Unilateral grade 3 or above)	33/110 (30.0%)	17/124 (13.6%)	*0.002*
Necrotising enterocolitis			
Definite NEC (Stage II or above)	21/110 (20.6%)	25/124 (20.2%)	0.937
NEC Stage III	8/110 (7.3%)	5/124 (4.0%)	0.280

Using either Student's t-test ($^+$) or χ^2-test, as appropriate

SRT – Surfactant replacement therapy, IVH – Intra-ventricular haemorrhage, RDS – Respiratory distress syndrome

major IVH (defined as Papile staging Grade III or above) from 30.0% in the early to 13.6% in the 1997-2002 more recent cohort (p=0.002). In fact, among the 20 deaths in ELBW babies related to IVH, a significant proportion (70%, 14/20) of them were born during 1993-1996.

Necrotising Enterocolitis (NEC) was classified according to the modified Bell's Staging Criteria. A definite case of NEC was taken as a baby with Stage II or above NEC as defined by the aforementioned criteria. No difference was found in the incidence of definite NEC between the two groups.

Chronic lung disease (CLD) was defined as oxygen dependency at 36-week post-conceptional age. The prevalence of CLD remained the same at around 50%, while the absolute number doubled in the second cohort as a result of improved survival. Nevertheless, the proportion of babies with severe chronic lung disease requiring home oxygen on discharge was similar, at around 10% in both groups.

In summary we demonstrated a significant decrease in morbidity including ROP and severe IVH in those babies born in the later period (1997-2003) compared with those born earlier (1993-1996). There was no significant difference in the proportion of ELBW survivors suffering from CLD or requiring home oxygen.

Length of Stay (LOS) in Hospital and Duration of Invasive Mechanical Ventilation

Among the survivors, there was a decrease in the median LOS from 108.5 days in the first period to 94.5 days in the second period (Table 5). Mean duration of invasive mechanical ventilation (defined as ventilation via endotracheal tube) was significantly shortened from 26.7 days to 16.7 days (p<0.001).

Early Neurodevelopment Outcomes of Survivors

All ELBW survivors were followed up by our long term follow up programme and had early neurodevelopment assessment at a mean corrected age of 19.0±2.2 months (mean±standard deviation). One hundred and twenty-six survivors were assessed, giving an average follow-up rate of 75.4%. There was no significant statistical difference in the follow-up rate between the two birth cohorts. The commonest reason for defaulting follow-up was emigration; others were loss of contact and parental refusal because the child was apparently healthy. There was no significant difference in neonatal morbidity including RDS, CLD, home oxygen dependency, PDA, ROP, early-onset sepsis, IVH and NEC between babies who attended follow-up and those who defaulted. In fact, the only statistically significant factor between the assessed and non-assessed groups was ethnicity (p<0.001). This is because a higher proportion of non-Chinese babies had left Hong Kong before they reached the age for assessment.

The enrolled children were assessed by our neurodevelopmental team using the Griffiths Mental Development Scales (Table 6). Hearing and visual function was assessed by an audiologist and optometrist respectively. Hearing impairment was defined by requirement for hearing aids. Children who were diagnosed as visually impaired included those who were blind or had refractive errors requiring spectacles. There was no significant difference in prevalence of cerebral palsy (CP) and hearing impairment between the two groups. It was not surprising that the more recent cohort of babies had a lower rate of visual impairment (5% as compared with 20%, p=0.008) as they also had a lower rate of ROP. Table 7 illustrates the assessment results from the Griffiths Mental Developmental Scales. The items of "very low" are categorised according to the standard score range equivalents for Griffiths scale scores that represent the proportion with scores less than 2 standard deviations.[9] Rates of low General Quotient and their sub-scores did not change significantly across the early and late cohorts. The proportions of survivors who needed early special education service (defined by the need to attend either the Integrated Child Care Centre or the Special Child Care Centre) dropped from 27.9% to 17.6%, though this was not statistically significant.

Table 5 Length of hospital stay among survivors

	1993-1996	**1997-2002**	***p*-value**
Length of stay (days)			
Mean (days)±SD	112.25±32.0	108.53±41.0	0.544
Range	49-438	51-338	
Duration of ventilation			
Mean±SD	26.7±21.0	16.7±18.2	0.001
Range	0-80	0-84	

Student's t-test was applied for comparison of means between the two cohorts.

Table 6 Neurological outcomes

Neurological outcomes among survivors	1993-1996 (% of assessed children)	1997-2002 (% of assessed children)	*p*-value
Total no. of children assessed	46	80	
Cerebral palsy	7 (15.2%)	10 (12.5%)	0.629
Visual impairment	9 (20.0%)	4 (5.0%)	0.008
Hearing impairment	3 (6.5%)	3 (3.8%)	0.464
Seizure	0 (0%)	1 (1.3%)	0.454
Hydrocephalus requiring shunt	1 (2.2%)	0 (0%)	0.178

Using χ^2-test or Fisher's exact test, as appropriate.

Table 7 Griffiths Developmental Scores and cognitive function

Griffiths Development Score & Use of Special Education Service			1993-1996 (% in assessed children)	1997-2002 (% in assessed children)	*p*-value
General Quotient	Total score	Very low (<75)	8 (19.0%)	13 (16.0%)	0.675
	Locomotor	Very low (<68)	8 (19.0%)	12 (14.8%)	0.546
	Personal-social development	Very low (<68)	7 (16.7%)	13 (16.0%)	0.930
	Hearing and Speech	Very low (<64)	3 (7.1%)	9 (11.1%)	0.750
	Coordination	Very low (<69)	2 (4.8%)	12 (14.8%)	0.136
	Performance	Very low (<65)	2 (4.8%)	9 (11.1%)	0.329
Need for Special Education Service			12 (27.9%)	12 (17.6%)	0.201

Using χ^2-test or Fisher's exact test, as appropriate.

"Very low" was defined as Griffiths Scale Scores ≤2 SD below mean

Discussion

Advances in obstetric and neonatal management have revolutionised the fate of ELBW infants. Their survival has improved dramatically over the past two decades.[10] Overall in the 1997-2002 cohort, the mortality rates were only 30% and 6.2% in babies with birth weights of "501-750 g" and "751-1000 g" respectively. The mortality of ELBW infants born at 24-27 weeks and 28-32 weeks were 17.1% and 3% respectively. Our results compared favourably with those of other large scale studies reported in recent years, including mortality data published by the Vermont Oxford Neonatal Network (our center is the only local center contributing to the Vermont Oxford Neonatal Network Data).[11-13]

There have been several important advances in perinatal practices in the past decade. In our study, the proportion of infants with a first-minute Apgar score less than or equal to three dropped from 48.1% in 1993-1996 to 29.0% in 1997-2002. Other perinatal centers have reported similar trends across the decade.[12] The first minute score is thought to be closely related to the obstetric cause, though with limitations.[14] The better 1-minute score that we report may be a reflection of improvements in perinatal care, which in turn contributed to improved neonatal survival rates and decreased morbidity.

The proportion of women who received a complete course of antenatal steroids doubled (35.5% to 66.1%) when comparing in the early and recent cohort. Since the first controlled trial of the use of antepartum glucocorticoid for the prevention of respiratory distress syndrome published more than 25 years ago,[15] studies confirmed that antenatal corticosteroid therapy reduces the incidence of RDS, neonatal death and IVH.[16,17] Furthermore, antenatal exposure to corticosteroid enhanced the efficacy of surfactant therapy.[17] Despite the more liberal use of prenatal steroids, more babies (81 vs 74) in the recent cohort were treated with surfactant, indicating the increase use of surfactant therapy for less severe RDS in recent years. This was related to the adoption of a protocol for early rescue therapy strategies for all babies who require assisted ventilation after birth The average duration of ventilation decreased significantly from 26.7 days in the early 1990s to 16.7 days in later years. The shorter length of ventilation period could be explained by the decrease in severity of RDS associated with increasing antenatal steroid use[12] and early administration of surfactant and other supportive measures. A similar trend has been observed by other members of the Vermont Oxford Network[12] who also reported that prolonged ventilation in ELBW babies was not only associated with increased mortality but was also

associated with poor long-term neurological outcomes among survivors.[18,19]

It is well established that the long-term neurodevelopmental outcomes of ELBW infants are generally worse than those born at full term.[20,21] It is estimated that at least 15-30% of them have significant neurosensory impairments. The rate varies depending on how handicap is defined and the nature of cohorts.[22,23] Factors that may contribute to this include the inherent vulnerability of the premature brain during a critical period of development, multiple clinical problems specific to prematurity, acute chorioamnionitis and stressful environmental conditions.[24] With improved overall survival, there are growing concerns about the steady increase in the absolute number of the infants with disabilities.[25] Our study showed that there was no increase in prevalence or number of survivors with adverse early neurodevelopment outcomes. We reported no significant changes in prevalence of cerebral palsy between the two study cohorts, which was consistent with the observations from other studies conducted within similar period.[6] The rate of cerebral palsy remained static at 12-15% throughout the decade. This figure compared favourably with the results reported in other developed countries which ranged from 7% to 30%.[26-29]

There was a significant decline of visual impairment from 19.6% to 4.9%. Depending on the definitions used, wide range of figures were reported by other groups that ranged from 6% to 23%.[26] This declining incidence is consistent with the significant drop in incidence of ROP across the epochs we reported, and is probably related to the reduction in average length of mechanical ventilation. The proportion of children with hearing impairment remained low at 3.7-6.5% throughout the whole study period. In general, our results were in agreement with those reported elsewhere.[6,27,28]

Several papers published in recent years have used Bayley mental and motor test scores to assess ELBW survivors at a corrected age of around 18-22 months. Depending on the mode of assessment and inclusion criteria of subjects, 30-50% of these children have been found to have a Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) of less than 70 (2 S.D. below the mean).[6,27,30] In our study, the proportion of patients with Griffiths total score and sub-scores below two standard deviations remained fairly constant at 19% and 16% respectively for the two periods. There was no increase in the number of survivors with a low score or need for special education service despite the increase in the total number of survivors.

It is important to emphasise that many aspects of neonatal intensive care have improved significantly over the last decade. In our unit, various improvement programmes were implemented at different stages during this study period. The provision of optimal nutritional support by early supplementary parenteral nutrition has improved growth and reduced morbidity. Infection control measures including hand hygiene promotion, a noscomial infection surveillance programme and the improved care of central intravenous catheters have reduced infection rates. Improved nursing care and monitoring of infants has also contributed to an overall improvement in survival and reduction in morbidity. Given the number of management strategies that have been improved and implemented over the recent decade it is difficult to quantify the contribution made of each individual strategy. Moreover, given the longitudinal design of our study we have not been able to demonstrate causation between each individual treatment and improved outcome. There are other limitations to our study. Some variables such as chorioamnionitis which is known to be associated with chronic lung disease and periventricular white matter disease that potentially affect the neurodevelopment outcome were not evaluated in our study. Furthermore, our study only reported neurodevelopment outcome at 18-20 months corrected age. Some researchers have cautioned that neurological findings in the early two years may be too optimistic. For example, a long term follow up study reported that a significant proportion of ELBW children classified as non-disabled at an early age may show impaired neurosensory functioning in later childhood or even adolescence.[26,31] However, the results of such long-term studies may not be able to accurately reflect the impact of altered perinatal management strategies implemented in recent years. The neurosensory functioning in the survivors deserves monitoring after discharge so that their families can receive proper counseling and rehabilitation services if necessary.

Conclusion

In conclusion, our study presents evidence of improving outcome, both in morbidity and mortality for ELBW infants cared for in our unit between two time periods (1993-1996 and 1997-2002). Besides changing use of surfactant therapy, other advances in perinatal and neonatal intensive care have contributed to the improved survival and decrease neonatal morbidity. Despite the improved survival of ELBW infants, there was no increase in the proportion and number of babies

with adverse early neurodevelopment outcomes. Long-term follow up of these survivors to school age is warranted to assess learning or other behavioural problems among the survivors. Apart from improvement in neonatal intensive care, prevention of premature birth and perinatal infection will play a pivotal role in further improving the survival and long-term outcome of extreme premature infants.

Acknowledgement

We would like to thank Dr. NS Tsoi, Dr. YK Ng, Dr. SL Lee, Dr. MS Wong and Dr. Stella Chim and all the nursing staff of the neonatal unit of Queen Mary Hospital and Tsan Yuk Hospital for providing care for all the babies, and Dr. Michelle Heys for providing editorial assistance.

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