Int. J. Prenatal and Perinatal Studies (1991) 45–53

Perinatal Factors and Relation to Mortality, Morbidity, and Neurodevelopmental Outcome in Preterm Infants

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Abstract

A cohort of 104 consecutive preterm ($\leq$ 34 weeks) infants requiring NICU admission was studied. In hospital mortality was 18% and could be significantly related to gestational age, birth weight, apgar score after one minute, HMD, pneumothorax, ICH, convulsions and IPPV ($P < 0.05$). Logistic regression analysis established asphyxia at birth (low apgar scores), birth weight, pneumothorax, ICH and convulsions to be significantly related to mortality. After 18 months major handicap had a higher incidence in girls than in boys. Perinatal transport seemed associated with minor handicap. Infants with both major and minor handicap had a higher incidence of squint but not of refractive errors or astigmatism. Twelve infants had impaired hearing. Following discharge 52 infants, whether normal or handicaped required subsequent hospitalization.

This study shows that follow up is important for preterm infants requiring NICU admission since the incidence of handicap is high irrespective of birth weight or gestational age.

Introduction

Follow-up of infants discharged from neonatal intensive care units (NICU) is very important, because of the high incidence of subsequent disabilities. Most reports concentrate on low birth weight [1] or make a comparison between two

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groups of infants, such as ventilated and non-ventilated infants [2], gender [3], influence of perinatal transfer [4], or gestational age and birth weight factors [5].

The purpose of this investigation was to establish the relation between perinatal risk factors in infants with a gestational age of $\leq$ 34 weeks and the incidence of mortality and morbidity at 18 months (corrected for prematurity). An additional aim was to evaluate the level of care at the NICU of the Free University Hospital, Amsterdam. The following perinatal determinants were considered: gestational age, birth weight, gender, type and location of delivery, perinatal transfer (in utero and after birth), apgar scores, premature rupture of membranes (PROM, $\geq$ 24 hours), hyaline membrane disease (HMD), pneumothorax, apnea, sepsis, convulsions, intermittent positive airway pressure (IPPV), continuous positive airway pressure (CPAP), intracranial hemorrhage (ICH) and persistent ductus arteriosus (PDA).

The neurodevelopmental findings at 18 months (corrected for prematurity) are presented for the surviving infants and the relation between handicap and perinatal risk factors was investigated.

Subsequent hospitalization after discharge and visual/hearing impairments are also reported.

Patients and Methods

Patients in Neonatal Period

The first 104 infants with a gestational age of $\leq$ 34 weeks admitted to the NICU after 1-10-1983 were included in the study. Of four infants who died within 6 hours of birth some data were not available. Eighty-five (82%) of the infants survived.

Following discharge the hospital records of all infants were reviewed, particularly the presence of PROM, gestational age, birth weight, gender, location of delivery, antenatal or postnatal transport, type of delivery and the apgar scores after birth. Neonatal data included the presence of HMD, pneumothorax, PDA, apnea, bacterial sepsis, ICH, convulsions and exposure to IPPV or CPAP.

The gestational age of the infants was derived from the maternal history of the last menstrual period and confirmed by clinical assessment of the infants [6]. If there was a discrepancy of more than three weeks the infants were excluded from the study.

ICH was detected by ultrasonography of the head [7] which was performed during the first weeks after birth, two to three times in the first week and twice in the following weeks, unless the infant was discharged or died. All infants were screened for ICH, except the four infants who died within 6 hours after birth. In these infants autopsy findings were recorded. Periventricular leucomalacia was not diagnosed during the study period, even on retrospective interpretation of the ultrasound images.

The one infant with chromosomal aberrations during the study was excluded.

Follow-up Protocol

Infants surviving the neonatal admission were examined for physical and neurodevelopmental examinations at 9 and 18 months postterm. All results were expressed in terms of age from the expected date of delivery (postterm age).

Screening for neurodevelopmental outcome was performed using the Denver developmental screening test (DDST)[8] with and without correction for preterm birth[9,10].

According to the outcome the infants were allocated to three groups: no handicap, minor handicap and major handicap. No handicap was designated as absence of retardation (a normal DDST uncorrected for prematurity) and no motor, visual or hearing disability. A minor handicap was diagnosed when some retardation was present (3–4 months retarded with the DDST uncorrected for prematurity) and/or at least one of the following; a mild neurological disorder, such as a hypotonia or hypertonia, mild visual or hearing defect. Such disabilities were unlikely to interfere with normal life. A major handicap was diagnosed when severe retardation was present (5 or more months retarded with the DDST uncorrected for prematurity) and/or at least one of the following; a severe neurological disorder, such as a cerebral palsy, severe visual or hearing defect. Such disabilities would probably seriously interfere with normal daily function.

Eye examinations were performed in the NICU for retinopathy of prematurity in all infants and at follow-up 88% of the infants underwent examinations in the pediatric ophthalmological department. For detection of squint the cover/uncover test and prism test were used. Refraction was determined by retinoscopy after installation of cyclopentolate 1%. Funduscopy was performed to exclude retinal abnormalities.

At 9 months postterm age the infants were screened for hearing loss with the Ewing screening test. Complete audiometric examinations were made in suspect cases.

At 18 months postterm age reasons for further hospitalization after discharge in the neonatal period were investigated.

Of the 85 surviving infants two did not attend follow-up: one died due to the cot-death syndrome aged 5 month; the parents of the second child refused to cooperate.

Statistical Methods

In the analysis of mortality the infants who died were contrasted with those who survived with respect to the different perinatal determinants. Firstly Student's t-test (two-tailed) for continuous determinants and Fischer's exact test (two-tailed) or chi-square test for discrete determinants were used to investigate the (univariate) association between a determinant and mortality. Because of interdependency between the different determinants a multivariate analysis was performed in second place. With stepwise logistic regression (using the statistical computer program BMDP-LR) the multivariate association between mortality and the determinants was studied. With this method a statistical model was built, in which successively the best explanatory determinants (according to some cri-

terion) were selected, adjusting for the ones already in the model and allowing for determinants, already in the model, to be removed again.

In the analysis of morbidity the infants, who survived and were still in the cohort after 18 months, were divided into three groups defined by handicap: no, minor and major handicap. Now only univariate comparisons were made, using analysis of variance (for continuous determinants) and the chi-square test (for discrete determinants).

Results

Mortality

The mean gestational age of the 104 preterm infants studied was 30.5 weeks (range 25–34 weeks) and the mean birth weight 1460 g (range 600–2650 g).

Table 1 shows the breakdown of perinatal risk factors for the group surviving and deceased infants. Table 2 shows the division of the factors for the healthy infants and infants with major or minor handicaps.

Nineteen infants died in the hospital during the admission to the NICU (in hospital mortality rate 18.3%). The mean birth weight of the deceased infants was 1220 g (range 640–1950 g), which was significantly lower compared with the mean birth weight of the surviving group (1514 g, $p = 0.012$). The mean gestational age of the infants who died (28.3 weeks, range 25–34 weeks) was also significantly lower compared with the mean gestational age of the surviving infants. (31.0 weeks, $p \leq 0.001$).

Comparison between infants who died and the remaining infants showed significant differences for the following perinatal determinants (Table 1): the apgar score after 1 min, HMD, pneumothorax, ICH, convulsions and IPPV. No significant difference was found for gender, type and location of delivery, presence of PROM, incidence of apnea, sepsis and PDA and the therapeutical use of CPAP.

Using stepwise logistic regression the simultaneous effect of the determinants on mortality was studied. The regression gave the following results. Starting with a model only containing a constant, were successively selected gestational age, convulsions, pneumothorax, apgar score, ICH and birth weight. At this step gestational age had a significance level of only 0.13, reflecting its interdependence with determinants already in the model (e.g. birth weight), and was removed from the model. The selected determinants all had significance levels of less than 0.05. None of the remaining determinants, including the ones which were found using the univariate approach, showed significant contributions.

Morbidity after 18 Months

Seven of the 83 infants followed-up had major neurodevelopmental sequelae (6.7% of the total group, 8.4% of the surviving infants). Cerebral palsy was the only major handicap.

Ten infants had a minor handicap. Three had slight sensoneural hearing loss, 3 had hypotonia and 1 hypertonia, one infant required revalidation due to talipes equinovarus. The two other infants showed a three months retarded neuro-

Table 1. Determinants for surviving and deceased infants.

	Surviving	Died	p*
Number	85	19	
Boys	50	11	
Girls	35	8	
Mean GA (weeks)	31.0 (26–34)	28.3 (25–34)	≤ 0.001
Mean BW (grams)	1514 (600–2650)	1220 (640–1950)	0.012
Location of delivery			
Own hospital	18	1	
Antenatal transfer	28	9	
Postnatal transfer	39	9	
Type of delivery			
Spontaneous	34	8	
Extraction	0	3	
Caesarean section	49	8	
Apgar score $1' \leq 4$	21	13	0.007
$5' \leq 6$	11	6	
PROM	16	3	
HMD	32	14	0.005
Pneumothorax	7	11	0.001
Apnea	26	4	
Sepsis	13	3	
Convulsions	3	7	0.002
IPPV	58	19	0.003
CPAP only	9	0	
ICH	21	15	≤ 0.001
PDA	21	8	

* Student's t test or Fisher exact test (two-tailed)
GA = Gestational Age
BW = Birth Weight
See text for other abbreviations

logical development at 18 months, established with the DDST uncorrected for prematurity.

The DDST was done with and without correction for preterm birth. In infants with a major handicap the results of the DDST was in the normal range when the age was corrected for prematurity. Only when the test was done without correction for prematurity were the results of the test for motor development abnormal in the infants with a handicap.

Analysis of the univariate association between morbidity and the discrete perinatal determinants using the chi-square test showed significance at the 5% level only for gender ($p = 0.04$). More girls than boys seemed to have a major handicap (Table 2). Near significance was reached for place of birth ($p = 0.06$). Studying the effect of gestational age and birth weight on morbidity by means of

Table 2. Perinatal factors related to healthy survivors and infants with major/minor handicaps.

	Healthy survivors	Major	Minor	p
Number	66	7	10	
Boys	40	1	7	
Girls	26[1]	6[1]	3	0.044
Mean GA (weeks)	31.2	30.9	29.9	
Mean BW (grams)	1533	1619	1265	
Location of delivery				
Own hospital	15[2]	0[2]	1[2]	0.063
Antenatal transfer	18[2]	3[2]	7[2]	
Postnatal transfer	33[2]	4[2]	2[2]	
Type of delivery				
Spontaneous	26	3	4	
Caesarean section	40	4	6	
Apgar score $1' \leq 4$	15	3	3	
$5' \leq 6$	8	2	1	
PROM	13	2	1	
HMD	24	4	4	
Pneumothorax	6	0	1	
Apnea	17	4	5	
Sepsis	10	0	3	
Convulsions	3	0	0	
IPPV	44	6	8	
CPAP only	8	0	1	
ICH	15	3	3	
PDA	18	2	1	

[1] $p < 0.05$ (Chi-square test)
[2] $p = 0.06$
GA = Gestational Age
BW = Birth Weight
See text for other abbreviations

analysis of variance no relation could be demonstrated ($p = 0.16$ for gestational age, $p = 0.20$ for birth weight).

Ocular examination was done in 73 infants (88% of the infants followed-up) (Table 3). The incidence of refractive errors and of astigmatism was the same in the three groups. There was a high incidence of squint in the total group (14%). The incidence of squint in the infants with a major and minor handicap was even higher (50% and 30% respectively) than in the infants with a normal development (7%).

In 55 of the 83 surviving infants who were followed-up (66%) a screening hearing test or an audiometric examination was made. When the screening test was not done we looked at the DDST to see if there was a possible hearing loss and performed a full audiometric examination. Nine infants had a conductive disturbance (16%). Three infants with a minor handicap had a sensoneural hearing loss.

Table 3. Results of ocular examination of surviving infants at the corrected age of 9 months.

	Total	Major	Minor
N	83	7	10
Ophtalmologic examination	73	6	10
Examination of refractive errors	70	4	10
Mean spherical equivalent			
Left eye	0.7 ± 1.0	0.7 ± 1.0	1.0 ± 0.9
≥ +2 Dioptrics	12	2	3
Right eye	0.7 ± 1.1	0.7 ± 1.1	0.8 ± 0.9
≥ +2 Dioptrics	11	1	3
Mean astigmatism			
Left eye	0.4 ± 0.9	0.5 ± 0.8	0.3 ± 0.9
> 1 Dioptric	8	1	1
Right eye	0.3 ± 0.8	0.3 ± 0.5	0.3 ± 0.9
> 1 Dioptric	7	0	1
Strabismus	10	3	3

Hospitalization between discharge in the neonatal period and 18 months of age was very frequent. Of the 83 infants followed-up 52 were admitted to hospital for a total of 90 times. Infants with a handicap were not more frequently hospitalized than infants with a normal development (9 infants with a handicap were hospitalized for a total of 17 times). The diagnoses of the infants who were hospitalized showed a high incidence of upper and lower respiratory tract infections (29% of all infants hospitalized) and the incidence of hospitalization due to inguinal hernia procedures was also high (19% of all infants hospitalized).

Discussion

As in many reports, gestational age and birth weight had predictable effects upon survival.

Convulsions also were related to mortality, although, surprisingly, infants surviving convulsions in the neonatal period had a normal development.

ICH was also associated with a higher mortality, though the neurodevelopmental outcome did not seem to be related to ICH. One explanation could be that the grade of ICH was much higher in the infants who died than in surviving infants. Periventricular leucomalacia was not diagnosed in the neonatal period. In 4 of the 7 infants with major handicap cerebral computer tomography was performed at 1 year age, in all 4 cerebral atrophy was found.

Asphyxia (low apgar scores) directly after birth and pneumothorax were also associated with a higher mortality, but had no further influence on surviving infants.

All other determinants found in the univariate way to be related to mortality were also related to the above mentioned determinants.

The finding that more girls had a major handicap is in contrast to other reports[3] showing that boys have a much higher mortality rate and a worse out-

come. In a study in our hospital of 517 infants with a birth weight below 1500 g a higher mortality and handicap rate in boys than in girls has also been confirmed (Personal communication).

Transported infants (antenatal or postnatal transfers) seemed to have a higher incidence of minor and major handicap. Marlow[4] concluded that there was the same risk for mortality and morbidity in infants followed-up in their own hospital as for transported infants. Our findings may not be in disagreement with his report, since he only considered the risk of transport and a major handicap.

The incidence of squint in our total population is similar to that of other studies[11]. A higher incidence of squint in infants with a handicap has not been reported. We looked at a population of infants with a birth weight below 1500 g and did not find a correlation between cerebral palsy and squint even though the incidence of squint in the total group was high (10%)[12].

Our finding of a poor correlation between the DDST corrected for gestational age and the neurodevelopmental outcome is in agreement with Elliman[9] and Miller[10].

The incidence of hearing disabilities in our group was lower than Bergmann[13] described, but he studied only infants with a birthweight below 1500 g.

The incidence of hospitalization after discharge was very high and this should be borne in mind, when infants are going home after their hospitalization in the neonatal period.

As in the study of Van Zeben et al.[14] we conclude that the morbidity of infants is irrespective of birth weight and gestational age. All infants, who needed intensive care after birth should be in a follow-up program, because of the considerable incidence of disability.

Abbreviations Used

NICU Neonatal Intensive Care Unit, ICH Intracranial Hemorrhage, HMD Hyaline Membrane Disease, PROM Premature Rupture of the Membranes, IPPV Intermittent Positive Airway Pressure, CPAP Continuous Positive Airway Pressure, PDA Persistent Ductus Arteriosus, DDST Denver Development Screening Test.

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