Neurodevelopmental outcome of babies weighing less than 2001 g at birth: influence of perinatal transfer and mechanical ventilation

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SUMMARY From 1976 to 1980, 1034 children who had weighed less than 2001 g at birth were cared for at the North Western regional neonatal intensive care unit. Of these, 315 babies were neonatal referrals and 91 were born in the unit after antenatal transfer from their district hospital. Significantly fewer of the babies referred as neonates survived ($n=167$, 53%) compared with 67 of the antenatal referrals (74%), and 490 of those born in the unit (78%). They also had a higher incidence of major handicaps (24 of 167, 14%) compared with six of 67 (9%) of the antenatal referrals and 35 of 490 (7%) of those born in the unit. To control for selection bias among neonatal referrals, the outcome of ventilated neonatal referrals was compared with that of ventilated babies born in the unit. The two groups were comparable for the incidence of a wide range of neonatal complications. No differences in rates of survival or handicap were found. We conclude that sick babies transferred after birth to regional neonatal intensive care units have similar short and long term outcomes to sick babies born in regional units.

From 1976–80 this hospital was the sole referral centre for intensive care of newborn infants in the North Western region. At its inception the neonatal referral service was directed towards the transport of babies deemed to require mechanical ventilation. During the same period an antenatal referral service evolved for the transfer of mothers with high risk pregnancies in which the need for neonatal intensive care was anticipated. In this paper we report the mortality and long term neurodevelopmental morbidity of low birthweight babies transferred in the perinatal period to our hospital, and relate these outcomes to the need for ventilatory support.

Patients and methods

We studied 1034 infants who were born alive weighing 2000 g or less between 1 January 1976 and 31 December 1980 who were cared for on the neonatal medical unit at this hospital. Mortality and neurodevelopmental outcome were analysed for three groups: babies who were referred as neonates ($n=315$), antenatal referrals ($n=91$), and babies who were born to mothers who booked for delivery at this hospital ($n=628$). The 'ventilated' subgroup comprised 386 babies who received more than four

hours mechanical ventilation through an endotracheal tube.

NEONATAL REFERRALS

The organisation of the neonatal referral service in the North Western region has been described previously.¹ Babies were transferred from 18 special care units (16 within the region). The median distance was 10.9 miles (range 2–100) and the median age at referral was 8.7 hours. Two hundred and eighty babies (89%) were referred within the first 48 hours and three (1%) after the 28th day. A primary respiratory illness was the reason for referral in 300 (95%) cases, prematurity alone being the indication in only two cases. No important complications developed during any of the journeys.

Details of each child's condition on arrival at the referring unit were recorded in 303 (96%) cases. Two hundred and two (67%) were judged to be in a stable condition. In the others the problems encountered were: central cyanosis ($n=47$), cyanosis and gasping ($n=16$), peripheral circulatory failure ($n=31$), untreated or inadequately drained pneumothorax ($n=7$), hypoglycaemia (blood glucose <1.5 mmol/l; $n=11$), and hypothermia (rectal temperature $<34^{\circ}\text{C}$; $n=27$). Only 20 infants were

breathing air spontaneously. Of the remainder, 149 were being given oxygen by headbox, 12 (4%) were receiving continuous positive airways pressure ventilation, and 117 (37%) were receiving intermittent positive pressure ventilation, including 47 (15%) who were being hand ventilated. Thirteen children were being managed unconventionally. During transfer 212 received mechanical ventilation through an endotracheal tube, 41 received continuous positive airways pressure ventilation by face mask, and 62 were breathing oxygen spontaneously by headbox.

ANTENATAL REFERRALS

One hundred and twelve pregnancies (126 unborn babies) were transferred during the study period. One infant was born during the ambulance journey, two were stillborn at this hospital, and four mothers were later returned to their referring units for delivery. Thirty infants weighed more than 2000 g at birth and are not considered further.

The main indications for antenatal referral were: pre-eclampsia (25%), premature rupture of the membranes or preterm labour (40%), intrauterine growth retardation (18%), and Rh haemolytic disease (18%). No influence on survival was observed when individual indications for transfer were considered. The median interval from antenatal transfer to delivery was 10.5 days. Three babies died in the delivery unit of extreme prematurity. Eighteen babies (20%) did not develop any neonatal complications and might therefore have been deemed unnecessary antenatal referrals.

Methods

Seven hundred and twenty four babies (70%) survived to be discharged home. Follow up information was obtained for 674 (93%) at a median (range) age of 3 years 3 months (2 years–6 years 9 months), including 20 children who subsequently died. Four further children died from acute neonatal illnesses after return to their referring units but before they

could be discharged home. These have been classified as deaths before discharge. The details of follow up have been described previously.² Of the survivors, 570 were examined and completed a psychometric test (NM), and information was abstracted from hospital or community follow up records for 56 other children. The parents of an additional 28 children who lived outside the north west replied in answer to a questionnaire that the children had no neurological or development problems.

For the purposes of this study we classified outcome into two groups: major neurodevelopmental handicap and normal. A major neurodevelopmental handicap comprised any of the following disabilities: cerebral palsy, developmental retardation (Griffiths quotient (GQ) or Wechsler intelligence quotient (IQ) of less than 70), blindness or deafness sufficient to warrant special schooling, and hydrocephalus.

The ages at follow up were calculated from the expected date of delivery. The significances of various comparisons were tested using the χ^2 test or the Mann-Whitney U test, as appropriate.

Results

PERINATAL TRANSFER AND OUTCOME

The proportion of babies surviving to be discharged home in the three study groups is shown in table 1. Among those with birth weights of 1251–2000 g, the survival rates in antenatal referrals and those babies born in this hospital were similar (83% and 88%, respectively), whereas neonatal referrals had a significantly lower survival rate (65%). In contrast, among babies weighing 500–1250 g, the survival rates of neonatal referrals and babies born in this hospital were similar (37% and 40%, respectively), and the differences in survival among the three groups were not significant.

Sixty five survivors (9%) had a major handicap. The incidence of handicap in the neonatal referrals (14%) was greater than that in babies born in this hospital (7.1%; $p<0.001$), and this difference was

Table 1 Survival by birth weight 1976–80

	Birth weight					
	500–1250 g		1251–2000 g		Total No <2000 g	
	No	No (%) of survivors	No	No (%) of survivors	No	No (%) of survivors
Neonatal referrals	133	49(37)	182	118(65)	315	167(53)
Antenatal referrals	32	18(56)	59	49(83)*	91	67(74)†
Born in hospital	145	58(40)	483	432(89)†	628	490(78)†

* $p<0.02$, and † $p<0.001$ compared with neonatal referrals.

seen among those with birth weights of 1251–2000 g ($p<0.01$) but not at 501–1250 g (NS). In contrast, in each birthweight group the incidence of handicap in antenatal referrals was similar to that among babies born in this hospital (table 2). Neither differences in survival nor in the incidence of handicap varied significantly when allowance was made for congenital abnormalities.

The incidence of individual major disabilities is shown in table 3. This table excludes 10 children whose handicaps were due to major congenital abnormalities described previously.² Cerebral palsy and developmental delay (GQ or IQ <71) were the commonest disabilities in all three groups. None of the six survivors with major handicap who had been referred antenatally were either deaf or blind. Deafness was found in a quarter of the handicapped survivors who had been referred as neonates compared with only 4% of handicapped survivors born in this hospital ($p<0.04$). Blindness was found in between 13 and 16% of the survivors in these two groups. There were no significant differences in the incidences of cerebral palsy, developmental delay, or hydrocephalus among the three groups, each of

which also had a similar mean number of disabilities/handicapped survivor, implying a similar degree of handicap in each group.

EFFECT OF MECHANICAL VENTILATION ON SURVIVAL AND HANDICAP

Mechanical ventilation exerted a major influence on outcome. Babies who were ventilated had a significantly lower survival rate and a higher incidence of handicap among survivors compared with the babies who were not ventilated (40% compared with 96.8%, and 18% compared with 4.7%, respectively). In addition, major differences between the study groups in their need for mechanical ventilation were found. A significantly higher proportion of neonatal referrals were ventilated (77%) than antenatal referrals (37%, $p<0.001$) or babies born in this hospital (24%; $p<0.001$). To what extent does the need for ventilation account for the differences in outcome between the neonatal referrals and the others?

Because only a small number of babies received ventilation after antenatal transfer ($n=34$) these were included with the babies born in this hospital

Table 2 Incidence of major handicap among survivors

	Birth weight					
	500–1250 g		1251–2000 g		Total No <2000 g	
	No	No (%) with major handicap	No	No (%) with major handicap	No	No (%) with major handicap
Neonatal referrals	49	12(25)	118	12(10)	167	24(14)
Antenatal referrals	18	3(17)	49	3(6)	67	6(9)
Born in hospital	58	11(19)	432	24(6)*	490	35(7)†

* $p<0.01$, and † $p<0.001$ compared with neonatal referrals.

Table 3 The incidence of individual disabilities in children with major handicaps

	Antenatal referrals ($n=6$) No (%)	Neonatal referrals ($n=24$) No (%)	Born in hospital ($n=25$) No (%)	Total ($n=55$) No (%)
Disability:				
Cerebral palsy	4(67)	12(50)	15(60)	31(56)
GQ or IQ: <50	2(33)	6(25)	5(20)	13(24)
51–70	3(50)	9(38)	7(28)	19(34)
Blindness	0	3(12)	4(16)	7(13)
Deafness	0	6(25)	1(4)	7(13)
Hydrocephalus	1(17)	5(21)	2(8)	8(14)
Mean number of disabilities/child	1.7	1.7	1.4	1.5
Associated impairments:				
Fits	2(33)	4(17)	6(24)	12(22)
Clumsiness	1(17)	4(17)	1(4)	6(11)

for further analysis. In addition, we have excluded children whose death ($n=36$) or major handicap ($n=10$) were directly attributable to a major congenital abnormality, and those babies born in this hospital who were not admitted to the neonatal medical unit but died on the delivery suite ($n=13$). All but one of the exclusions were born in this hospital.

For ventilated babies within each birthweight category no differences in survival or incidence of handicap were found between the ventilated neonatal referrals and babies born in this hospital (table 4). Babies born in this hospital who required ventilation were more likely to have had a lower Apgar

score at 1 minute ($p<0.001$), or to have received intubation in the delivery room ($p<0.001$) compared with ventilated neonatal referrals. Otherwise the incidence of a wide range of neonatal illnesses was similar between the two ventilated groups, who also received ventilation and oxygen treatment for a similar length of time (table 5).

For babies who were not ventilated, within each birthweight category no differences in survival were found between the neonatal referrals and babies born in this hospital. Among those of 1251–2000 g birthweight, however, more surviving neonatal referrals were handicapped (11% compared with 3.4%, $p<0.05$). In contrast, for birthweights

Table 4 Survival, and incidence of major handicap in survivors in babies who were ventilated and those who were not

	Birth weight 500–1250 g			Birth weight 1251–2000 g		
	Total No	No (%) of survivors	No (%) with handicap	Total No	No (%) of survivors	No (%) with handicap
Babies ventilated:						
Neonatal referrals	103	30(29)	10(33)	133	73(55)	7(10)
Born in hospital	99	24(24)	8(33)	71	36(51)	4(11)
Babies not ventilated:						
Neonatal referrals	23	19(83)	2(10)	46	45(98)	5(11)*
Born in hospital	61	51(84)	4(8)	439	436(99)	15(3)

* $p<0.05$ compared with those born in unit.

Table 5 Comparison of frequency of perinatal events between those born in unit and neonatal referrals for babies who were ventilated and those who were not

	Ventilated babies		Babies not ventilated	
	Neonatal referrals ($n=236$) No (%)	Born in hospital ($n=170$) No (%)	Neonatal referrals ($n=69$) No (%)	Born in hospital ($n=500$) No (%)
Apgar score <3 at 1 minute	89(38)	97(57)	15(22)	123(25)
at 5 minutes	27(11)	28(16)	2(3)	18(4)
Intubated at delivery	104(44)	118(69)***	17(25)	141(28)
Infant respiratory distress syndrome	181(77)	120(70)	44(64)	38(8)***
Congenital pneumonia	27(11)	21(12)	13(19)	27(5)***
Early apnoea (<72 hours)	19(8)	10(6)	10(14)	27(5)**
Late apnoea	34(14)	28(16)	16(23)	32(6)***
Pneumothorax	96(41)	58(34)	2(3)	3(1)
Patent ductus arteriosus	36(15)	28(16)	8(12)	12(2)***
Chronic lung disease	14(6)	9(5)	1(1)	0
Early onset of sepsis	56(24)	40(24)	18(26)	41(8)***
Late onset of sepsis	89(38)	58(34)	23(33)	74(15)**
Fits	44(19)	25(15)	4(6)	12(2)
Other abnormal neurological symptoms	60(25)	52(30)	9(13)	25(5)*
Median (range) duration of ventilation	2.1 days (1–52)	2.4 days (1–40)		
Median (range) duration of oxygen treatment	5.4 days (1–150)	6.3 days (0–363)†		

* $p<0.02$; ** $p<0.01$; *** $p<0.001$; † one baby ventilated with air for apnoea.

500–1250 g similar proportions in each group survived with handicap (table 4).

To necessitate neonatal transfer a baby must have developed a severe illness. Neonatal referrals who were not ventilated had high frequencies of adverse perinatal events compared with babies born in this hospital who were not ventilated (table 5). This is reflected in the high incidence of later handicap in the referred group.

Discussion

Geographically based studies have shown that babies who are born and cared for in a perinatal intensive care centre have significantly higher survival rates compared with babies who are born at district obstetric units, even if they are subsequently transferred.^{3 4} Our observation of a higher mortality and incidence of handicap among babies transferred in the neonatal period compared with antenatal referrals or babies born in this hospital is consistent with these findings. One further study observed that intraventricular haemorrhage was more common among neonatal transfers,⁵ though more recent data suggest that this may not be so.⁶ We have, however, taken the analysis further by examining specific subgroups of the referred patients and those born in this hospital, according to whether or not they received mechanical ventilation. In addition, we used both survival and neurodevelopmental handicap as outcome measures, because the quality of survival is as important as survival itself.

Babies who are transferred in the neonatal period are highly preselected by the exclusion of, firstly, those who die in the first few hours after birth; secondly, those who develop no postnatal complication and, thirdly, by the exclusion of those pregnancies in which preterm delivery is anticipated and transfer to the regional centre effected. Thus in the absence of a properly randomised, controlled trial it is difficult to assess objectively the additional risk to a small baby of delivery outside the regional centre and subsequent transfer when severe neonatal illness occurs. The simple reporting of geographically based data (as has been advocated) will not answer this question.

When all babies were considered it was at first surprising that the differences in survival and handicap between neonatal referral, antenatal referral, and those born in this hospital were least marked for those in the 500–1250 g birthweight group. The antenatal referral and born in this hospital groups, however, were biased in as much as they comprised both those babies who, being extremely small, died soon after birth in the delivery room, and those babies who developed no major

complications, thereby invalidating comparison with neonatal transfers.

The comparison of ventilated babies in the group referred and those born in this hospital is a logical attempt to control for preselection. The outcome for ventilated infants was clearly worse than for those who did not need such support, and a much higher proportion of neonatal referrals required ventilation. Even so, the ventilated babies born in this hospital had lower Apgar scores at 1 minute and a higher incidence of intubation in the delivery room than the neonatal referrals, implying that they were in poorer condition at birth. None the less, in both ventilated groups the time course of the respiratory illness and the incidence of postnatal complications were remarkably similar, suggesting that the severity of neonatal illness was similar. When the two ventilated groups were compared no differences in survival or incidence of major handicap were observed.

Surviving neonatal referrals who were not ventilated had a higher incidence of handicap compared with babies born in this hospital and not ventilated. These neonatal referrals, however, are quite different from the other babies who were not ventilated, as they suffered from a variety of serious neonatal illnesses necessitating referral. These neonatal referrals had a much higher incidence of clinical risk factors compared with the group born in this hospital who were not ventilated (table 5), these being mostly healthy preterm babies.

Babies born in this hospital who were not ventilated and weighed 1251–2000 g formed the largest group in this study. Therefore, despite having the lowest handicap rate of any group discussed, in real terms they made a substantial contribution to handicap among infants weighing 2000 g or less, as they made up 27% of the handicapped children.

The range of disabilities encountered among survivors varied slightly between the groups, with the obvious exception that deafness was more common among survivors after neonatal transfer. The reason for this difference and its clinical significance are not clear. The cause of deafness among low birthweight survivors is uncertain and probably multifactorial.⁷ This disability has not been previously associated with neonatal transfer.

Despite the striking similarities in both clinical course and outcome for the two groups of ventilated babies, however, the populations are still not identical: transferred babies were in significantly better condition at birth (table 4). There remains the possibility that lung disease among neonatal transfers may have been worsened by suboptimal care before referral, as only 67% were judged to be in satisfactory condition when they arrived. This, together

with intubation for transfer, may have resulted in babies receiving long term mechanical ventilation that would not have been necessary had they been born and managed in the regional centre.

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References

- ¹ Chiswick ML, Davies P, Bate R, Dryburgh E, Gordon-Nesbitt D. Regional organisation of neonatal intensive care in the North-West. *Br Med J* 1979;i:247-50.
- ² Marlow N, D'Souza SW, Chiswick ML. Neurodevelopmental outcome in babies less than 2001 g birthweight. *Br Med J* 1987; **294**:1582-6.
- ³ Cordero L, Backes CR, Zuspan FP. Very low-birthweight infant I: influence of the place of birth on survival. *Am J Obstet Gynecol* 1982;**143**:533-7.
- ⁴ Lobb MO, Morgan MEI, Bond AP, Cooke RWI. Transfer before delivery on Merseyside: an analysis of the first 140 patients. *Br J Obstet Gynaecol* 1983;**90**:338-41.
- ⁵ Clark CE, Clyman RI, Roth RS, *et al.* Risk factors of intra-ventricular haemorrhage in low-birthweight infants. *J Pediatr* 1981;**99**:625-8.
- ⁶ Beverley D, Foote K, Howel D, Congdon P. Effect of birth-place on infants with low birthweight. *Br Med J* 1986;**293**:981-3.
- ⁷ Marlow N, Chiswick ML. Neurodevelopmental outcome in extremely low birthweight survivors. In: Chiswick ML, ed. *Recent advances in perinatal medicine*. Vol II. Edinburgh; Churchill Livingstone, 1985:181-205.

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