Improved survival and neurodevelopmental outcome after prolonged ventilation in preterm neonates who have received antenatal steroids and surfactant

E A Gaillard, R W I Cooke, N J Shaw

Abstract

***Aims*—To assess survival and neurodevelopmental outcome following prolonged ventilation beyond 27 or 49 days of postnatal life in neonates treated with antenatal steroids and surfactant.**

***Methods*—The medical records of 84 babies born in 1994–1996 requiring ventilation after 27 postnatal days at Liverpool Women's Hospital were reviewed to determine the duration of mechanical ventilation, survival, and neurodevelopmental outcome at 3 years of age.**

***Results*—Fifty six babies were mechanically ventilated after 27 postnatal days but for less than 50 days; 48 (86%) survived to 3 years. Twenty six (54%) of the survivors had normal neurodevelopment at 3 years and seven (15%) had only mild disability. Twenty eight babies were ventilated after 49 postnatal days; 14 survived to 3 years. Five of these survivors were neurodevelopmentally normal at 3 years and two had mild disability.**

***Conclusions*—Survival decreases with more prolonged ventilation. When antenatal steroids and postnatal surfactant are used, there appears to be improved survival and neurodevelopmental outcome in preterm babies who require prolonged ventilation.**

(*Arch Dis Child Fetal Neonatal Ed* 2001;**84**:F194–F196)

Keywords: prolonged ventilation; preterm; neurodevelopmental outcome; survival

There are few reports on mortality and neurodevelopmental outcome in neonates after prolonged ventilation. Two studies[1 2] have shown length of ventilation to be a better predictor of long term intact survival than findings on cranial ultrasound scan. Wheater *et al*[1] reported high mortality (83%) and no neurodevelopmentally normal survivors in a cohort of 12 very low birthweight babies ventilated for 50 days or more, and 29% mortality (29% normal survivors at 18 months) for 35 babies ventilated for 28–40 days. Bozynski *et al*[2] found mechanical ventilation for more than 21 days to be significantly associated with poor performance on the Bayley Mental Development Index compared with intracranial haemorrhage in 159 surviving babies of less than 1200 g until 18 months of age, when the difference was no longer significant. In addition, prolonged ventilation was associated with lower birth weight and gestational age. Overstreet *et al*[3] reported 35% mortality in 58 babies ventilated by day 60 of age. In contrast, Luchi *et al*[4] found no significant correlation between duration of mechanical ventilation and adverse neurological outcome at 36 months in a cohort of 27 babies with a mean birth weight of 940 g and mean gestation of 27 postmenstrual weeks ventilated for 22–128 days (44% were normal at 3 years and 22% had major disability). The babies in these studies were all born in 1980–1992 and most of them were not treated with antenatal steroids or exogenous surfactant. More recently, Whitfield *et al*[5] reported functional outcome data for 115 children at school age with a birth weight of less than 800 g born in 1974–1985, and found no significant difference overall between functional outcome categories for number of days of ventilation, days of oxygen treatment, or days in the intensive care unit. That study was, however, not primarily looking at outcome following prolonged ventilation.

Since the advent of surfactant treatment[6] and antenatal steroid use,[7] there has been increased survival of extremely preterm neonates and at the same time the incidence of parenchymal cerebral haemorrhage and cerebral palsy in these babies may have decreased.[8–13] The aim of this study was to determine the neurodevelopmental outcome in a population of neonates who had received antenatal steroids and surfactant and who required prolonged mechanical ventilation.

Methods

All babies born between 1 January 1994 and 31 December 1996 ventilated for more than 27 days at Liverpool Women's Hospital were identified from their discharge letters. Babies were excluded if they were transferred from another hospital after the first postnatal week (mostly surgical referrals) or ventilated beyond 27 postnatal days after a surgical procedure requiring an anaesthetic.

From the medical records, number of days that mechanical ventilation was required was determined, and the number of completed days off the ventilator during this period were recorded. Any periods of less than 24 hours off the ventilator were included in the number of ventilator days. All babies had serial cranial ultrasound scans and from these records the worst cranial ultrasound scan appearance was determined. Cranial ultrasound was graded in

Liverpool Women's Hospital, Liverpool L8 7SS, UK
E A Gaillard
R W I Cooke
N J Shaw

Correspondence to:
Dr Shaw, Regional Intensive Care Unit, Liverpool Women's Hospital, Crown Street, Liverpool L8 7SS, UK
Ben.Shaw@lwh-tr.nwest.nhs.uk

Accepted 9 January 2001

Table 1 Functional categorisation of infants at follow up at 3 years of age

1	Normal: no clinically apparent neurodevelopmental abnormality causing functional disability
2	Mild disability: for example, myopia, language delay, mild hearing loss, hyperactivity, or motor clumsiness
3	Moderate disability: for example, spastic diplegia, hemiplegia, or moderate learning disability (developmental quotient 50–69)
4	Severe disability: for example, spastic quadriplegia, blindness, deafness (loss of 70 decibel or more), uncontrolled epilepsy, or severe learning disability (developmental quotient <50). Infants with multiple disabilities

Groups 3 and 4 can be considered together as major disability.

Table 2 Basic and clinical data for infants receiving prolonged ventilation

	Ventilated beyond 27 (but not 50) postnatal days	*Ventilated beyond 49 postnatal days*
Number	56	28
Male (%)	32 (57)	14 (50)
Median gestation (range) in weeks	26 (23–34)	26 (23–33)
Median birth weight (range) in g	852 (520–2710)	745 (580–1620)
Median time to first extubation in days (range)	17 (0–49)	21 (1–108)
Median number of total ventilator days (range)	30 (7–49)	44 (19–108)
Cranial ultrasound, normal or grade 1, subependymal haemorrhage only (%)	34 (61)	12 (43)
Grade 2, intraventricular haemorrhage with or without ventricular dilatation (%)	12 (21)	12 (39)
Grade 3, parenchymal haemorrhage (%)	10 (18)	4 (14)
Cystic periventricular leucomalacia (%)	10 (18)	5 (18)
Ventriculo-peritoneal shunt (%)	5 (9)	3 (11)

Table 3 Neurodevelopmental outcome and survival at 3 years of infants receiving prolonged ventilation according to length of ventilation

	Ventilated beyond 27 (but not 50) postnatal days	*Ventilated beyond 49 postnatal days*
Total	56	28
Alive (%)	48 (86)	14 (50)
Neurodevelopment (% of survivors)		
Normal	26 (54)	5 (36)
Mild disability	7 (15)	2 (14)
Moderate disability	11 (23)	4 (29)
Severe disability	4 (8)	3 (21)

the following way: normal; grade 1, subependymal haemorrhage only; grade 2, intraventricular haemorrhage with/without ventricular dilatation; grade 3, parenchymal haemorrhage.

After discharge, babies are routinely followed up at least yearly after the first year of life, until aged 5, and neurodevelopmental progress is assessed using the classification in table 1[14] The neurodevelopmental outcome at 3 years was determined from these follow up data.

Results

One hundred babies born between 1 January 1994 and 31 December 1996 were ventilated beyond 27 postnatal days. The medical records of 92 babies were reviewed; the remaining eight could not be traced and have been excluded from the study. For a further eight infants, neurodevelopmental data at three years could not be obtained (seven of these had normal cranial ultrasound or subependymal haemorrhage only, and one had grade 2 haemorrhage). These babies were also excluded. Twenty eight babies (14 male) were ventilated beyond 49 days of postnatal life and 56 (32 male) were ventilated beyond day 27 but not beyond day 49. Fifty four babies had a total of 96 attempts at extubation resulting in staying off ventilation for 24 hours or more at some time in the first 4 weeks.

During the period of study, about 75% of mothers in preterm labour before 34 weeks gestation received antenatal steroids. All but one baby received two doses of exogenous surfactant. Table 2 gives basic and clinical data for the babies included in the study.

Sixteen babies (19%) died on the neonatal intensive care unit and six babies died after discharge. Sixty two babies (74%) survived to 3 years of age; table 3 gives the neurodevelopmental outcome. Thirty one babies (50% of survivors) were neurodevelopmentally normal at 3 years of age, nine (15%) had mild disability, and 22 (35%) had major disability (15 with moderate and seven with severe disability).

Table 4 shows neurodevelopmental outcome according to length of ventilation and number of days off the ventilator during the first 27 and 49 days. There was a (non-significant) trend towards babies who were off the ventilator longer having an improved chance of survival.

Discussion

In recent years the use of antenatal steroids and postnatal surfactant has been associated with improved survival in preterm infants.[6 7] At the same time the rate of parenchymal cerebral haemorrhage and rate of cerebral palsy in these infants may have decreased.[8–13] Studies on infants not treated with surfactant have suggested a poor outcome after prolonged ventilation.[1–3] The aim of this study was to assess survival and neurodevelopmental outcome at 3 years of age in babies who, after treatment with antenatal steroids and surfactant, required prolonged ventilation after 27 postnatal days. To our knowledge this is the first study of this kind in infants who have all received surfactant (although babies born more recently included in the study by Wheater *et al*[1] received surfactant (J Rennie, personal communication)). The survival rate of 73% for our cohort is similar to that reported by Cooke[8] in 521 very low birthweight infants born in 1990–1993, although our incidence of major disability appears slightly higher than reported in this study. This may be explained by the

Table 4 Neurodevelopmental outcome and survival at 3 years of infants receiving prolonged ventilation according to length of ventilation and number of days off ventilator (0, 1–7, or >7)

	Ventilated beyond 27 (but not 50) postnatal days			*Ventilated beyond 49 postnatal days*		
	0	*1–7*	*>7*	*0*	*1–7*	*>7*
Total	18	17	21	5	8	15
Alive (%)	13 (72)	15 (88)	20 (95)	1 (20)	4 (50)	9 (60)
Neurodevelopment (% of survivors)						
Normal	8 (44)	7 (41)	11 (52)	1	1	3
Mild disability	2 (11)	2 (12)	3 (14)	0	2	0
Moderate disability	3 (17)	4 (24)	4 (19)	0	0	3
Severe disability	0	2 (12)	2 (10)	0	1	3

higher rate of parenchymal cerebral haemorrhage in our cohort.[15–17]

Extreme prematurity was strongly associated with the requirement for prolonged ventilation. Compared with previous antenatal steroid and surfactant studies reporting survival and disability following ventilation for less than 50 days, we have found in a larger group of babies than previously studied a higher percentage (54%) of neurodevelopmentally intact survivors. Mild disability was found in 15%, which was unlikely to have been detected at 18 months. It is therefore likely that our neurodevelopmental outcome is considerably better (69% intact or mild disability) than that reported by Wheater *et al*[1] (10 (40%) normal among 25 survivors at 18 months). The neurodevelopmental outcome in our study is only slightly better than that of Luchi *et al*,[4] who reported 10 (45%) neurodevelopmentally normal survivors at 36 months in a cohort of 22 babies of birth weight 1200 g or less and ventilated for between 22 and 60 days.

Comparison of survival and neurodevelopmental outcome for babies ventilated after 49 postnatal days is difficult as the numbers are small. However, whereas Wheater *et al*[1] reported no normal survivors among 12 very low birthweight babies ventilated for 50 days or more, there were five out of 14 (36%) normal survivors at 3 years in our cohort. Luchi *et al* reported that out of five survivors who had been ventilated for more than 60 days, two were neurodevelopmentally normal at 3 years.

The improved outcome (both survival and neurodevelopmental) in our cohort of babies is likely to be due to the use of antenatal steroids and exogenous surfactant. With interrupted ventilation, there was a trend towards a better outcome than for babies who did not spend any time off the ventilator. This may be because the more mature and less sick neonates spent more time off the ventilator.[18 19] Also, interrupted ventilation is more likely to occur when ventilatory support is used for lack of respiratory drive or apnoea rather than severe lung disease.

We conclude that, when antenatal steroids and postnatal surfactant are used, there is improved survival in babies who had required prolonged (beyond 27 days) and very prolonged (beyond 49 days) mechanical ventilation. Neurodevelopmental outcome is also better than previously reported. This information will be useful when advising parents about the prognosis of their baby if they are ventilator dependent beyond 27 days.

1 Wheater M, Rennie JM. Poor prognosis after prolonged ventilation for bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed* 1994;**71**:F210–1.
2 Bozynski ME, Nelson MN, Matalon TA, *et al*. Prolonged mechanical ventilation and intracranial hemorrhage: impact on developmental progress through 18 months in infants weighing 1,200 grams or less at birth. *Pediatrics* 1987;**79**:670–6.
3 Overstreet DW, Jackson JC, van Belle G, *et al*. Estimation of mortality risk in chronically ventilated infants with bronchopulmonary dysplasia. *Pediatrics* 1991;**88**:1153–60.
4 Luchi JM, Bennett FC, Jackson JC. Predictors of neurodevelopmental outcome following bronchopulmonary dysplasia. *American Journal of Diseases in Children* 1991;**145**:813–17.
5 Whitfield MF, Grunau RV, Holsti L. Extremely premature (< or = 800 g) schoolchildren: multiple areas of hidden disability. *Arch Dis Child Fetal Neonatal Ed* 1997;**77**:F85–90.
6 Kresch MJ, Clive JM. Meta-analyses of surfactant replacement therapy of infants with birth weights less than 2000 grams. *J Perinatol* 1998;**18**:276–83.
7 Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. *Am J Obstet Gynecol* 1995;**173**:322–35.
8 Cooke RW. Trends in incidence of cranial ultrasound lesions and cerebral palsy in very low birthweight infants 1982–93. *Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F115–17.
9 Aziz K, Vickar DB, Sauve RS, *et al*. Province-based study of neurologic disability of children weighing 500 through 1249 grams at birth in relation to neonatal cerebral ultrasound findings. *Pediatrics* 1995;**95**:837–44.
10 Sheth RD. Trends in incidence and severity of intraventricular hemorrhage. *J Child Neurol* 1998;**13**:261–4.
11 Robertson CM, Hrynchyshyn GJ, Etches PC, *et al*. Population-based study of the incidence, complexity, and severity of neurologic disability among survivors weighing 500 through 1250 grams at birth: a comparison of two birth cohorts. *Pediatrics* 1992;**90**:750–5.
12 Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. *Early Hum Dev* 1999;**53**:193–218.
13 Tudehope D, Burns YR, Gray PH, *et al*. Changing patterns of survival and outcome at 4 years of children who weighed 500–999 g at birth. *J Paediatr Child Health* 1995;**31**:451–6.
14 Cooke RW. Factors affecting survival and outcome at 3 years in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1994;**71**:F28–31.
15 Pinto-Martin JA, Riolo S, Cnaan A, *et al*. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. *Pediatrics* 1995;**95**:249–54.
16 Whitaker AH, Feldman JF, Van Rossem R, *et al*. Neonatal cranial ultrasound abnormalities in low birth weight infants: relation to cognitive outcomes at six years of age. *Paediatrics* 1996;**98**:719–29.
17 de Vries LS, Rademaker KJ, Groenendaal F, *et al*. Correlation between neonatal cranial ultrasound, MRI in infancy and neurodevelopmental outcome in infants with a large intraventricular haemorrhage with or without unilateral parenchymal involvment. *Neuropediatrics* 1998;**29**:180–8.
18 Johnson A, Townshend P, Yudkin P, *et al*. Functional abilities at age 4 years of children born before 29 weeks of gestation. *BMJ* 1993;**306**:1715–18.
19 Marlow N, Roberts BL, Cooke RWI. Motor skills in extremely low birthweight children at the age of 6 years. *Arch Dis Child* 1989;**64**:839–47. <th;2>