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Neonatal complications of extreme prematurity in mechanically ventilated infants

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Abstract. Previous data have suggested that neonatal complications amongst preterm ventilated infants increase with decreasing gestational age and thus are likely to be greatest among ventilated infants of less than 28 weeks gestational age. The aim of this study was to test that hypothesis, thus we report the neonatal complications of 175 extremely preterm mechanically ventilated infants (gestational age ≤ 28 weeks). Of the infants 152 were ventilated because of respiratory distress syndrome (RDS) or respiratory distress of severe prematurity, 41% of these infants died. Amongst infants with RDS or respiratory distress of extreme prematurity, mortality was significantly increased in infants of gestational age ≤ 24 weeks and birth weight ≤ 1000 g. In this group 20% developed a pneumothorax, and mortality was inversely related to gestational age. In infants with RDS, 43% developed a periventricular haemorrhage and 37% were still oxygen-dependent at 28 days of age; neither of these complications was significantly related to birth weight or gestational age. Of infants with RDS 38% developed a patent ductus arteriosus and 16% developed retinopathy of prematurity. These data suggest that even amongst very immature infants there has been an impressive reduction in the neonatal complications of mechanical ventilation.

Key words: Mechanical ventilation – Prematurity – Pneumothorax – Patent ductus arteriosus – Intracerebral haemorrhage

Introduction

Mechanical ventilation is an essential part of treatment for very immature infants. Survival of this group of patients has improved over recent years, and as a consequence even infants born as early as 22 weeks gestation are considered viable. A review of the neonatal outcome of ventilated preterm infants, which mainly included those born at a gestational age greater than 27 weeks, suggested that the complications of mechanical ventilation may increase with decreasing gestational age [6]. It seems likely that infants born at less than or equal to 28 weeks gestation, who require respiratory support, may be at higher risk of both mortality and morbidity. Unfortunately, to date this hypothesis has not been tested and although there are some data [2, 12] on the outcome of very immature infants, no study has concentrated exclusively on infants born very preterm who have required mechanical ventilation. We have now therefore assessed the neonatal outcome of such a group of patients since these results have important implications for counselling parents and determining the intensive care needs of such patients in the future.

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Abbreviations: CLD = chronic lung disease; NEC = necrotizing enterocolitis; NICU = neonatal intensive care unit; PDA = patent ductus arteriosus; PVH = periventricular haemorrhage; RDEP = respiratory distress of extreme prematurity; RDS = respiratory distress syndrome

Patients and methods

The outcome of all inborn and outborn infants of ≤ 28 weeks gestational age was reviewed. They were admitted to and ventilated on the neonatal intensive care unit during the 3 year period January 1987–December 1989 inclusive. Gestational age was determined from maternal menstrual dates, antenatal ultrasound examination and physical examination of the neonate using the Dubowitz score, if there was a discrepancy between these three methods, greatest reliance was placed on the data from the early antenatal ultrasound examination. During the 3-year period the only major change in management policy was the introduction of surfactant replacement therapy in November 1989, but only six infants included in this report were recruited into that trial.

On the neonatal intensive care unit (NICU) 175 infants of gestational age ≤ 28 weeks were ventilated. Their median gestational age was 26 weeks (range 22–28) and median birth weight 840 g (range 398–1710). Twenty-eight of the infants (median gestational age 28 weeks, range 25–28) were small for dates, that is, their birth weight was less than the 10th percentile when related to gestational age. During the same time period only nine infants admitted to the NICU of ≤ 28 weeks gestational age were never ventilated, their median gestational age was 28 weeks (range 26–28), none of this group died.

The majority (87%) of infants ($n = 152$) were ventilated because of respiratory distress syndrome (RDS) or respiratory dis-

tress of extreme prematurity (RDEP). RDS was diagnosed if the infant developed respiratory distress prior to 4 h of age, with a symmetrical ground glass appearance on the chest X-ray film [6], and no infectious agent was isolated in the first 48 h of life. If the infant fulfilled the above criteria but was less than 24 weeks gestational age, he or she was classified as suffering from respiratory distress of severe prematurity. Congenital sepsis was diagnosed if a single bacterial species was isolated from the gastric aspirate and surface swabs, with or without positive blood cultures. This definition was used as some of the mothers received antibiotics prior to delivery which may have interfered with the results of the neonatal cultures. Congenital pneumonia was diagnosed if the infant had respiratory distress, the chest X-ray film demonstrated asymmetrical shadowing and organisms were isolated from the tracheal aspirate. Apnoea was diagnosed if the infants had poor respiratory drive, as evidenced by repeated cessations of respiratory effort for 15-s intervals without a chest X-ray film abnormality. Pulmonary hypoplasia was diagnosed if an infant required high peak pressures ($> 30\,cmH_2O$) both for resuscitation and during ventilation for at least the 1st week of life and this was associated with a chest X-ray film demonstrating small volume lungs. In those infants who died the diagnosis was confirmed on post mortem examination by a reduced lung weight and a radial alveolar count less than 4 [1]. Transient tachypnoea of the newborn was diagnosed if the infant's spontaneous respiratory rate exceeded 100/min and the chest X-ray film demonstrated prominent ill-defined vascular markings, oedematous interlobar septa and pleural effusions in the costophrenic angles and interlobar fissures typical of interstitial oedema, in the absence of a cardiac abnormality. During the 3-year period, no infant of gestational age ≤ 28 weeks was ventilated because of meconium aspiration syndrome, hypoxic ischaemic encephalopathy or surgically correctable congenital abnormalities.

The complications of mechanical ventilation were recorded. These included pneumothorax and chronic lung disease, defined as an oxygen requirement at 28 days of age in association with an abnormal appearance of the chest X-ray film. Serial cranial ultrasound scans were performed in the first 48 h of life and subsequently, at least weekly, to diagnose periventricular haemorrhage. Patent ductus arteriosus was diagnosed by clinical criteria [6] and then confirmed by echocardiography. All preterm infants who had been oxygen-dependent were examined by an ophthalmologist from 28 weeks postconceptional age to determine the occurrence of retinopathy of prematurity. Necrotizing enterocolitis was diagnosed if the infant had abdominal distension, bloody stools and an abdominal X-ray film which showed distended loops with or without pneumatosis coli.

Infants ≤ 28 weeks gestation were routinely ventilated in the labour suite unless they established vigorous respiratory efforts within 2 min with a heart rate > 100/min. They would then remain ventilated until admitted to the NICU. Non-intubated infants would be ventilated on the NICU if they developed recurrent apnoeic attacks or their blood gases deteriorated ($pO_2 \leq 50$ mmHg despite a high inspired oxygen concentration $FiO_2 \geq 60\%$ and/or $pCO_2 > 50$ mmHg associated with a pH < 7.25). Infants were ventilated via oral 2.0 or 2.5 mm endotracheal tubes using Sechrist IV ventilators. Mechanical ventilation was commenced at a rate of 60 breaths/min and a peak pressure sufficient to cause visible chest wall expansion [5]. Ventilator rates were increased if the infant's breathing was visibly asynchronous. Infants were only paralysed (pancuronium 100 μg/kg prn) if breathing remained asynchronous, despite increasing the ventilator rate up to 150 breaths/min [7]. In paralysed infants the ventilator rate would then be reduced to 60 breaths/min to avoid airtrapping [15].

All infants were nursed in humidified incubators. During the acute phase of the respiratory illness they received intravenous fluids at an initial rate of 40 ml/kg per 24 h. Intravenous fluids were usually slowly increased guided by the urine osmolality, daily serum electrolytes and changes in body weight. In some very immature infants very large quantities of intravenous fluid were needed even in the first 48 h of life (up to 200 ml/kg per 24 h to maintain appropriate fluid balance. Intravenous feeding was usually commenced at 48 h of age and, once the infant's respiratory status was stable, enteral feeding was started even in those who remained ventilated. The infants were fed with breast milk for at least the 1st week. Subsequently they would be continued on breast milk if in sufficient supply, if not, they would be changed to a low birth weight formula.

Analysis

The occurrence of major complications was related to the infant's gestational age, birth weight and diagnosis. To assess whether differences in the frequency of complications were statistically significant in infants of different maturity and birth weight groups, the chi-square test or Fisher's exact test were used. To assess if the relationship of occurrence of a neonatal complication to birth weight or gestational age was significant, a Spearman's correlation coefficient was calculated.

Results

Of the 175 infants ventilated from birth, 2 had recurrent apnoea and 5 had deteriorating blood gases. Of these patients, 152 infants suffered from RDS or RDEP, 6 had pulmonary hypoplasia (confirmed on post mortem examination in 4 cases), 4 had sepsis (all had positive blood cultures), 3 pneumonia, 5 apnoea and 5 transient tachypnoea of the newborn.

The overall mortality was 41% and the mortality rate of the small for dates infants was 75%. Of the infants ventilated for RDS or RDEP, 41% died (Table 1). In the RDS-RDEP group mortality was inversely related to gestational age (Table 2), this trend reached statistical significance if infants of 27 and 28 weeks gestation were compared with those of ≤ 24 weeks ($P = 0.003$). Mortality was significantly increased in infants of birth weight ≤ 1000 g ($P = 0.006$) (Table 3).

Of the infants with RDS or RDEP 20% developed a pneumothorax. There was no trend towards a greater frequency of air leak with decreasing maturity, however, in infants with pneumothorax the mortality increased with decreasing gestational age; 50% at 27–28 weeks gestation, 92% at 25–26 weeks and 100% at ≤ 24 weeks (Table 2). Though the frequency of pneumothorax was not significantly related to birth weight, mortality in infants with pneumothorax was significantly increased in

Table 1. Causes of death *(n)*

	RDS or RDEP	Other diagnoses
Total number of babies	152	23
Total number of deaths	63	9
Extreme prematurity ≤ 24 weeks	4	2
Periventricular haemorrhage	9	1
Respiratory failure	35	0
Pulmonary haemorrhage	4	0
Renal failure	0	0
Necrotizing enterocolitis	5	0
Septicaemia	6	1
Pulmonary hypoplasia	0	4
Congenital heart disease	0	1

Table 2. Complications of respiratory distress syndrome or respiratory distress of extreme prematurity related to gestational age

	Gestational age (weeks)		
	27–28 ($n = 72$)	25–26 ($n = 50$)	≤ 24 ($n = 30$)
Outcome			
Deaths	21 (29%)	23 (46%)	19 (63%)
Pneumothorax	16 (22%) (8)[a]	12 (24%) (11)	3 (10%) (3)
PVH	26 (36%) (10)	26 (52%) (15)	13 (43%) (6)
CLD	21 (29%) (4)	22 (44%) (5)	13 (43%) (3)
PDA	28 (39%)	19 (38%)	10 (33%)
Retinopathy of prematurity	5 (7%)	13 (26%)	7 (23%)
NEC	7 (10%)	5 (10%)	2 (7%)

[a] ( ) Number of infants who died

Table 3. Complications of RDS or RDEP related to birth weight

	Birth weight (g)		
	1001–1500 ($n = 51$)	501–1000 ($n = 96$)	≤ 500 ($n = 4$)
Outcome			
Deaths	13 (25%)	47 (49%)	3 (75%)
Pneumothorax	14 (27%) (9)[a]	17 (18%) (13)	0
PVH	20 (38%) (9)	43 (45%) (21)	2 (50%) (1)
CLD	15 (29%) (4)	40 (42%) (8)	1 (25%) (0)
PDA	22 (42%)	35 (36%)	0
Retinopathy of prematurity	3 (6%)	21 (22%)	1 (25%)
NEC	4 (8%)	10 (10%)	0

The outcome of the infant whose birth weight was > 1500 g is not displayed on this table

[a] ( ) number of infants who died

infants with birth weights 1001–1500 gms ($P = 0.001$) and birth weights ≤ 1000 g ($P = 0.02$).

Of infants with RDS or RDEP 43% developed periventricular haemorrhage (PVH). The severity of PVH ranged from unilateral subependymal haemorrhage to bilateral intraventricular haemorrhage with ventricular dilation and parenchymal extension. There was no significant trend of the presence of PVH or the effect of PVH on mortality, with gestational age or with birth weight.

Of infants with RDS or RDEP 37% developed chronic lung disease (CLD). The development of CLD was not significantly related to either gestational age or birth weight, nor was mortality significantly increased in infants with CLD. Twenty-seven infants were still oxygen-dependent at a postconceptional age of 36 weeks; the majority, 20, were born at a gestational age of less than 27 weeks and 22 had a birth weight less than 1000 g.

Of infants with RDS or RDEP 38% developed a patent ductus arteriosus (PDA). The occurrence of PDA did not relate significantly to either maturity or birth weight. In 17 cases the PDA resolved spontaneously but 33 infants required treatment with indomethacin and in seven infants the ductus was ligated.

Of the infants with RDS or RDEP 16% developed retinopathy of prematurity and this was more common in infants ≤ 26 weeks than > 26 weeks gestational age ($P = 0.006$). Retinopathy of prematurity was more common in infants with birth weight ≤ 1000 g compared to those with birth weight > 1000 g ($P = 0.018$). Of the babies with RDS or RDEP 9% developed necrotizing enterocolitis (NEC). The occurrence of NEC was not significantly related to gestational age or to birth weight.

Of the infants ventilated for diagnoses other than RDS or RDEP, 9 died, 5 developed pneumothoraces, 7 PVH, 2 CLD, 2 PDA and 1 retinopathy of prematurity. There were no cases of NEC in this group.

Discussion

The overall survival of the present group of infants who were ventilated for RDS was 59%, this is similar to the survival rate of 65% reported by Greenough and Roberton [6]. We included a greater number of infants born at less than 24 weeks of gestation, in whom mortality is higher, than the previous study [6] and this is likely to have influenced our results. Our infants were all ventilated and thus likely to be sicker than those included in earlier studies which reported mortality rates of (55% in 1976–1980 [12]; 48% in 1980–1984 [2]; and 44% in 1981–1985 [12]. These data suggest that survival rates of even very immature infants are continuing to increase slowly with time.

Our incidence of pneumothorax (20%) contrasts very favourably with that reported previously (39%) [6]. It is tempting to speculate that this reduction in the occurrence of air leak is due to the introduction of fast rate ventilation, to promote synchrony [8–10] used in association with selective paralysis of only those infants who fail to synchronize despite increase of the ventilator rate.

PVH remains a common complication in these preterm infants. Phillip et al. [20] suggested the incidence of PVH in infants of less than 35 weeks gestational age and birth weight less than 1500 g is decreasing. Our incidence of 48% in infants of less than 27 weeks gestational age compared to 61% in a previous report [6] supports that hypothesis. The occurrence of PVH was not related to

gestational age as had been found previously [4] but pneumothorax was a common association [15], 69% of infants with an air leak developing an PVH.

Of our series 37% developed CLD. It is difficult to compare this figure to those reported from different series which have included different study populations. When related to birth weight, the reported incidence of CLD varies from 5% [2] to 75% [19]. Our infants were all very immature and ventilated and thus the highest risk group, we therefore feel our incidence is encouragingly low. However, 27 of our infants, were still oxygen dependent at 36 weeks post conceptional age. This group is likely to suffer chronic respiratory morbidity and may even need home oxygen therapy [11]. The prevention of such chronic oxygen dependency is thus a major challenge.

Previous reports have demonstrated that the incidence of PDA in infants with birth weight less than 1000 g is 77% [22] and 81% [3]. Only 38% of our infants developed this condition, this may be explained by our policy of restricting fluid in the acute stage of RDS. Differences in the methods of diagnosis of PDA may also account for differences in the incidence of PDA in the present and previous studies [3, 22]. Administration of exogenous surfactant has recently been implicated in increasing the occurrence of PDA [21]; only six infants were so treated in the present study.

Retinopathy of prematurity has been reported to be especially common in infants of 29–33 weeks gestational age [17]. In the report a significant association was demonstrated with immaturity and low birth weight and the occurrence of retinopathy of prematurity. Our finding of only 16% of retinopathy of prematurity in infants of less than or equal to 28 weeks gestational age is therefore encouraging.

The occurrence of NEC is increased in infants of lower birth weight and gestation. This may explain the relatively large proportion of infants with NEC in the present study compared to the 0.95% reporting rate quoted by Palmer et al. [18]. Some of our infants were certainly from a high risk group [13], but we had hoped this may have been counteracted by our early use of small volumes of breast milk [16].

These results demonstrated that the majority of very immature infants survive and do not develop neonatal complications. The small group of infants who remain chronically oxygen dependent however have important implications for use of neonatal intensive care facilities. An accurate method of predicting the likelihood of this complications would be an extremely useful tool which would help to provide informed counselling of parents.

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