Comparing minimally invasive and proactive initial management of extremely preterm infants

A Lando (alando@dadlnet.dk), K Kure Østergaard, G Greisen
Department of Neonatology, The Juliane Marie Centre, University Hospital Copenhagen, Rigshospitalet, Copenhagen, Denmark

Interruption

Between 1986 and 2005, we followed a minimally invasive treatment strategy for all preterm infants in our department. This included avoiding intubation in the delivery room if possible, early nasal CPAP, and the INSURE (intubation-surfactant-extubation) strategy if the a/A ratio exceeded 0.22 until 1994 (1) or 0.36 thereafter (2). Mechanical ventilation was reserved for infants who developed respiratory insufficiency and was only used for extremely preterm infants after renewed consultation with their parents (3). Over the years, we became concerned that sometimes rescue mechanical ventilation was being provided too late and experience from Sweden suggested that an early active approach was associated with lower mortality rates in the most immature infants (4). In 2005, we decided to introduce an early active strategy for infants with a gestational age <26 weeks if the parents agreed. This involved providing intubation and prophylactic surfactant in the delivery room, followed by mechanical ventilation until the infant was clinically stable. At the same time, we also introduced gestational age-specific guidelines on general care during the first days of life.

Because a more active approach may allow survival of infants with greater risk of brain injury and hence increase the rate of psychomotor deficit, we planned a systematic follow-up. We decided to use a parental questionnaire as we did not have the capacity to carry out formal development tests, for example, using the Bayley Scales of Infant Development, and because we were keen to identify an increased incidence of psychomotor deficit early.

Parental questionnaires, such as the Ages and Stages Questionnaires (ASQ) (5) employed in this study, are increasingly being used, as parents know their children well and studies have proved that they are reliable when it comes to judging their children's actual abilities (6,7). There are ASQ questionnaires for 19 different ages, ranging from 4 to 60 months, and each consists of six questions in each of the following five domains: communication skills, gross motor skills, fine motor skills, problem-solving skills and personal-social skills. Each of the six questions provides scores ranging from zero for 'no', five for

Key notes
- In 2005, we changed our minimally invasive departmental policy for infants born before 26 weeks to a proactive approach to initial management in the delivery room. At the same time, we provided structured guidelines on the general care.
- The periods before and after the introduction of the policy were compared.
- Psychomotor development at 18 months did not change significantly, but the use of mechanical ventilation increased from 64% to 87% (p < 0.0001), and mortality fell from 46% to 36% (p = 0.06).
Ventilation during the two periods 1999 to mechanical ventilation and the days of mechanical ventilation during their first week of life in 1999 and 2005–2011 were calculated using the departmental clinical discharge database. Again we selected, without specific exclusions, the infants with a gestational age of <28 weeks born in our hospital or admitted from other hospitals during the first week of life.

The 2005–2011 data showed a discrepancy of 40 infants in the routine clinical discharge database and the dedicated follow-up database. We know that 11 of the babies died, but did not attempt to explore the reason for this difference further, because we could not do the same for the 1999–2003 follow-up data. Therefore, the results in this report on survival and use of mechanical ventilation are based on the hospital discharge database, whereas the results on neurodevelopmental outcome are from the specific 1999–2003 and 2005–2011 databases developed for the two studies.

Statistics: SPSS version 19 was used to calculate the z-score of the ASQ total score using the regression coefficients from the Danish national reference to correct for age (9). The two time periods were compared by the t-test and the chi-squared test as appropriate.

Table 1: Mortality and use of mechanical ventilation in the periods 1999–2003 and 2005–2011, calculated from the departmental discharge clinical database (GA = gestational age)

| GA (weeks) | Infants (N) | Mortality† | Infants in ventilator | Ventilator days in those ventilated (mean and range) |
|------------|-------------|------------|-----------------------|-----------------------------------------------------|
| < 26        | 188         | 87 (46%)   | 120 (64%)**           | 10.7 (1–76)                                         |
| 26 and 27   | 247         | 45 (18%)   | 107 (43%)***          | 6.6 (1–72)                                          |
| 2005–2011   | 203         | 74 (36%)   | 177 (87%)**           | 17.2 (1–100)                                        |
| < 26        | 252         | 40 (16%)   | 127 (50%)***          | 10.1 (1–97)                                         |

†Inborn and outborn admitted who died before discharge/admitted inborn and outborn × 100.

*p < 0.0001.

**p = 0.13.
Table 2 shows the 2005–2011 ASQ z-scores and the 1999–2003 ASQ z-scores at nine and 18 months of corrected age for infants born with a gestational age of <26 weeks and at 26 and 27 weeks. There were 85 nonresponders who did not fill out the ASQ 24-month questionnaire in the 2005–2011 group. We were able to contact 70 by telephone, but 15 could not be reached. The mean gestational age in the responder and nonresponder groups was the same (Table 3). More children in the nonresponder group (17%) were not able to walk independently at the corrected age of 18 months than the number of children who scored zero in the gross motor domain of the ASQ (7%). By the time of the telephone interviews, just two of the 70 children – aged 27 and 44 months corrected age – were not able to walk (Fig. 3). The percentage of children in the ASQ group who had a total ASQ score of <−1 SD was equal to the percentage of children who received extra help in day care or school (Table 3).

**DISCUSSION**

The change of delivery room policy was followed by a marked increase in the use of mechanical ventilation and perhaps contributed to improved survival rates among infants with a gestational age of <26 weeks. It was reassuring that there was no evidence of increased psychomotor deficit. While the risk of ASQ score below −2 SD showed a small increase from 22% to 26%, the mean z-score improved from −1.3 ± 2.2 to −0.8 ± 1.8, indicating overall an unchanged risk of developmental deficit.

There were only few surviving infants with a gestational age of 23 weeks in both groups and no infants with a gestational age of 22 weeks. Our results were calculated on inborn and outborn infants admitted to our department...
within their first week of life and, in spite of the more proactive approach in the latter period, the number of admissions did not change significantly.

Our study has some strengths. Firstly, it was planned as a quality control measure, using the previous 1999–2003 study as a reference, and was put in place when the change of policy was implemented. Secondly, parental questionnaires are unbiased in the sense that parental judgments are unlikely to be influenced by knowledge of the nature of the comparison.

This quality control measure is possible, due to the low cost and simplicity of parental questionnaires, even when hospitals do not routinely provide formal developmental testing. This model may be of interest to others working in similar conditions and deciding on major changes in treatment policy. However, it should be noted that even comparing 5-year periods in a relatively large neonatal unit will have limited statistical power to detect changes.

The comparison with the 1999–2003 data from our unit had limitations, apart from the limited statistical power. The previous reference study was carried out at one point in time, and, as a result, the children varied in age, from 12 to 60 months. The follow-up rate in the 1999–2003 cohort was higher, perhaps because the study included a telephone interview with questions on maternal education and child handicap. Furthermore, the reference group in 1999–2003 was local, not national, with a considerably higher maternal education. The analysis may have overcorrected for this difference and, as a result, the estimated deficit may have appeared smaller than it really was.

The main weakness is the relatively low follow-up rate. This is partly a result of the structure of the neonatal service in our region, where extremely preterm infants are transferred to step-down units before they are discharged home and these units are responsible for follow-ups. The children only return to us for a few appointments and some parents may think these are unnecessary and decide not to attend. Most of the nonresponders in the 18-month follow-up group were contactable by phone and, although there was some evidence of more motor delay or abnormality in this group, few were severely motor disabled and their cognitive skills did not appear to be too different. Overall, this was reassuring. We did not attempt to include the nonresponders in the 1999–2003 comparison group because a similar telephone interview was not carried out in the previous study.

Comparing the risk of deficits of 22% and 26% in the two groups to the international literature requires some explanation. First, we used a cut-off of $\leq 2 SD$, which in principle corresponds to what is usually termed moderate developmental disability, while $< -3 SD$ may correspond to severe developmental disability. Furthermore, the international literature often uses a complex concept of neurodevelopmental disability (NDI), including sensory disability. Blindness and deafness, however, typically contribute little to the rate of NDI and therefore it is relevant to compare disability rates with our data. In the UK (10) and Sweden (11), the combined categories of moderate and severe overall disability and moderate or severe neurodevelopmental deficits in infants born before a gestational age of 26 weeks were 29% and 33%, respectively (Fig. 4). It should be noted that these were multicenter studies comprising a much larger number of infants in a geographically defined area and that the children were evaluated at older age, which might have resulted in more children in the moderate impairment group. Cognitive performance tests carried out in children with the corrected age of 18–24 months are not a reliable way to predict outcome in individual children, whereas tests carried out at the corrected age of 5 or even 8 years are better (12,13).

| Study          | Mortality | NDI       |
|----------------|-----------|-----------|
| RH 2005–11     | 11%       | 22%       |
| RH 1999–03     | 13%       | 26%       |
| EPI Cure-2 2006| 12%       | 20%       |
| EXPRESS 2004–07| 10%       | 18%       |

Figure 4 Comparison of mortality and neurodevelopmental impairment (NDI) in three centres. Infants with gestational age of <26 weeks. RH: neonatal department, Rigshospitalet, Copenhagen. Mortality: death in neonatal care. NDI: ASQ total points at 18 months’ corrected age $\leq 2 SD$. EPI Cure-2 2006 (10). Mortality: death in neonatal care. NDI: nonimputed data on infants at median 34 months’ corrected age. EXPRESS 2004–2007 (11,22). Mortality: death in neonatal care and up to 365 days. NDI: infants at 30 months’ corrected age.
However, those children who are severely impaired at 2 years of age remain severely impaired at 5 or 8 years (12,14) and, more importantly for a quality control measure, the rate of deficit does not typically change much.

It is important to identify warning signals without undue delay. However, in our study, the ASQ score at a corrected age of 9 months showed a considerably lower incidence of deficit of 12%. Sutton et al. (15) found that by 1 year, only 11% of children born with a gestational age of 23–27 weeks had major mental deficits. This may suggest that the age of assessment should not be pushed below 12 months.

Is it at all likely that the change in policy would cause increased risk of psychomotor deficit? We were concerned for two reasons. Firstly, a more active early attitude could lead to increase the use of mechanical ventilation – which it did in our study – and mechanical ventilation carries a risk of inadvertent hyperventilation and brain injury (16,17). Secondly, potentially more immature and/or ill infants may survive – which is likely to have happened in our study – and these are more likely to survive with brain injuries than the more mature and less ill infants. Major randomised studies and meta-analyses on early intubation versus expectant management have been published in recent years (18–21). Although the number of infants aged <26 weeks are limited in these studies, there is currently nothing to suggest that prophylactic surfactant strategy provides short-term or long-term benefits when it comes to outcomes such as death or BPD.

We think that the trend towards increased survival in our 2005–2011 cohort is not likely to be explained by the prophylactic surfactant strategy in itself, but was more likely caused by a generally more proactive approach. This included a more structured protocol for the delivery management and care of these small infants, with a focus on resuscitation, thermoregulation, early intravenous parenteral nutrition and management of hypoglycaemia. Finally, parents expressed a wish for an active approach in the great majority of cases and this may well have encouraged us to be more proactive in the following days. As a result of this interpretation, we recently changed our approach back to avoiding intubation in the delivery room if possible.

CONCLUSION

Using parental questionnaires as a follow-up tool in a neonatal department is an easy and cost-effective way to monitor performance. We were able to demonstrate that a major change in policy regarding delivery room management of infants born before 26 weeks did not result in a major increase in psychomotor deficit. However, the use of mechanical ventilation increased significantly and survival tended to improve.

References
1. Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen B, Lundstrom K, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med 1994; 331: 1051–5.
2. Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks’ gestation. Pediatrics 1999; 105: e24.
3. Greisen G. Managing births at the limit of viability: the Danish experience. Semin Fetal Neonatal Med 2004; 9: 453–7.
4. Hakansson S, Farooqi A, Holmgren PA, Serenius F, Högborg U. Proactive management promotes outcome in extremely preterm infants: a population-based comparison of two perinatal management strategies. Pediatrics 2004; 114: 58–64.
5. Squires J, Potter L, Bricker D. The ASQ user’s guide for the Ages and Stages Questionnaires: a parent completed child-monitoring system. Second ed. Baltimore: Brookes Publishing Company, 1999.
6. Skellern CY, Roberts Y, O’Callaghan MJ. A parent-completed developmental questionnaire: follow up of ex-premature infants. J Paediatr Child Health 2001; 37: 125–9.
7. Kerstenjs JM, Bos AF, ten Vergert EM. Support of the global feasibility of the ages and stages questionnaire as developmental screener. Early Hum Dev 2009; 85: 443–7.
8. Plomgaard AM, Hansen BM, Greisen G. Measuring developmental deficit in children born at gestational age less than 26 weeks using a parent-completed developmental questionnaire. Acta Paediatr 2006; 95: 1488–94.
9. Østergaard KK, Lando AV, Hansen BM, Greisen G. A Danish reference chart for assessment of psychomotor development based on Ages and Stages Questionnaire. Dan Med J 2012; 59: A4429.
10. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPI Cure studies. BMJ 2012; 345: e7961.
11. Serenius F, Källen K, Blennow M, Ewald U, Fellman V, Holmström G, et al. Neurodevelopmental outcome in extremely preterm infants at 2, 5 years after active perinatal care in Sweden. JAMA 2013; 309: 1810–20.
12. Marlow N, Wolke D, Melanie A, Bracewell MA; Muthanna Samara for the EPI Cure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2006; 352: 19–27.
13. Roberts G, Anderson PJ, Doyle LW; the Victorian Infant Collaborative Study Group. The stability of the diagnosis of developmental disability between ages 2 and 8 in a geographic cohort of very preterm children born in 1997. Arch Dis Child 2010; 95: 786–90.
14. Lalal B. Prediction of neurodevelopmental outcome after preterm birth. Review article. Pediatr Neurol 2009; 40: 413–9.
15. Sutton L, Bajuk B. Population-based study of infants born at less than 28 weeks’ gestation in New South Wales, Australia, in 1992–3. New South Wales Neonatal Intensive Care Unit Study Group. Paediatr Perinat Epidemiol 1999; 13: 288–301.
16. Greisen G, Vannucchi RC. Is periventricular leucomalacia a result of hypoxic ischaemic injury? Hypocapnia and the preterm brain. Biol Neonate 2001; 79: 194–200.
17. Topp M, Uldall P, Greisen G. Cerebral palsy births in eastern Denmark, 1987–90: implications for neonatal care. Paediatr Perinat Epidemiol 2001; 15: 271–7.
18. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet J-M, Carlin JB; for the COIN Trial Investigators. Nasal CPAP or Intubation at birth for very preterm Infants. N Engl J Med 2008; 358: 700–8.
19. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptok AR, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010; 362: 1970–9.

20. Fischer HS, Bührer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013; 132: e1351–60.

21. Schmölzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung P. Non-invasive versus invasive respiratory support in preterm infants at birth. Systematic review and meta-analysis. *BMJ* 2013; 347: 1–8.

22. The EXPRESS group. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 2009; 301: 2225–33.