Clinical Research Report

Outcome of infants born at <32 weeks’ gestation in a single-centre level III neonatology unit – relation to feeding strategy

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Abstract

Objective: This study aimed to determine survival, neonatal morbidity, and outcomes at 1 and 2 years in children who were born very preterm, and to analyse any relation to enteral feeding.

Methods: We performed a prospective, observational study on very preterm infants (range: 23–31 weeks’ gestation) born at Innsbruck Medical University Hospital, Austria, between 2007 and 2014 (n = 557).

Results: The overall survival rate was 94.6%. Survival rates were 77.8%, 78.6%, 90.9%, and 90.9% among those born at 24, 25, 26, and 27 weeks, and 97.3%, 95.3%, 98.3%, and 100% among those born at 28, 29, 30, and 31 weeks of gestation, respectively. The overall prevalence of chronic lung disease among survivors was 7.3%. The prevalence of necrotizing enterocolitis requiring surgery, intraventricular haemorrhage grades 3 and 4, and severe retinopathy of prematurity was 3.1%, 2.1%, and 6.2%, respectively. There was no difference in short-term morbidity or neurodevelopmental outcome at 1 or 2 years of corrected age between infants who were fed with human milk at discharge and those who were formula-fed.

Conclusion: In the current study, mortality and short-term morbidity rates were low. No differences regarding feeding strategy were detected.
Introduction

The number of neonates surviving very preterm birth has gradually increased because of advances in perinatal and neonatal care. However, increasing survival is associated with an increased awareness of morbidity outcomes in these children.

Most of the large cohort studies that reported the outcome of very preterm-born children exclusively focussed on mortality and short-term morbidity of those born before 27 weeks’ gestation.\(^1\),\(^2\) Even though children who are born between 27 and 31 weeks have a lower relative risk for adverse outcomes, they comprise a much larger proportion of preterm births, and in absolute numbers, they account for most children with deficits.\(^3\) Therefore, up-to-date and reliable population-based information on outcome including the very preterm group is of special importance for caregivers.

The use of human milk compared with preterm infant formula in very preterm infants (born < 32 weeks’ gestation) during hospitalization is associated with reduced in-hospital morbidity. This morbidity includes lower rates of necrotizing enterocolitis (NEC),\(^4\)–\(^6\) chronic lung disease (CLD), and severe retinopathy of prematurity (ROP),\(^6\) as well as improved neurodevelopmental outcomes.\(^7\),\(^8\) Therefore, the effect of the enteral feeding strategy during the hospital stay should be considered in analyses of outcome data.

Therefore, this study aimed to report survival rates and survival without short-term morbidity in all live-born very preterm infants in a geographically defined area. We also included data on neurodevelopmental outcomes at 1 and 2 years old and focused on the effect of feeding strategy on outcome data.

Methods

Participants

The study survey area was Tyrol, which is a state in western Austria with 750,000 inhabitants and approximately 7500 live births per year. All infants who were born before 32 completed weeks of pregnancy at Innsbruck Medical University Hospital, which is the only neonatal intensive care unit in the geographical region, were enrolled. The study period was between January 2007 and December 2014.

The follow-up study was approved by the ethics committee of the Medical University of Innsbruck (No. AN2013–0086 333/4.2). Informed consent of the participants was not required because the database only contained routine data.

Maternal and neonatal data

The following clinical data were prospectively collected: maternal and neonatal data, including maternal age, maternal years of education, smoking during pregnancy, antenatal steroid use, gestational age (full weeks of gestation), birth weight (g), small for gestational age (SGA), multiple births, sex, postnatal surfactant use, diagnosis of early- and late-onset sepsis, CLD, intraventricular haemorrhage (IVH),
NEC, and severe ROP. Gestational age was calculated from the first day of the last menstrual period. This was compared with assessment of gestational age by ultrasound scans that were performed before 24 weeks. If there was a difference of more than 1 week between menstrual and ultrasound assessment, assessment of the scan was preferred. Growth charts developed by Fenton et al. were used to classify infants as SGA at birth. SGA was defined as a birth weight lower than the 10th percentile for sex and gestational age. Overall mortality was defined as all deaths that occurred after birth and included delivery room and neonatal intensive care unit deaths. Smoking habits during pregnancy (yes/no) were based on self-reported data. All data are available on request.

**Short-term outcome**

The following major short-time morbidities were analysed. Moderate/severe CLD was defined as oxygen dependence at 36 weeks’ postmenstrual age. NEC was defined according to Bell’s criteria and classified as medical (clinical symptoms and signs plus evidence of pneumatosis on an abdominal x-ray) or surgical (histological evidence of NEC on surgical specimens of the intestine). IVH was classified according to the method of Papile et al. Cystic periventricular leukomalacia (PVL) was defined by ultrasonographic findings that suggested cystic degeneration of periventricular white matter. ROP was graded according to international classification. A diagnosis of early-onset (≤72 hours after birth) or late-onset (>72 hours) sepsis required signs of generalized infection, a positive blood culture, and antibiotic therapy for 5 or more days.

An adverse short-term outcome was defined as moderate/severe CLD, NEC requiring surgical treatment, IVH grades 3 to 4, and ROP grades 3 to 5.

**Long-term outcome**

Neurodevelopmental outcome was assessed at 1 and 2 years of corrected age. Neurodevelopmental outcome was determined by neurological examinations and the Bayley Scales of Infant and Toddler Development, second edition (Bayley-II), for infants born between 2007 and 2013, and the third edition (Bayley-III) for infants born in 2014. Bayley-II scores provide psychomotor (PDI) and mental (MDI) developmental indices, Bayley-III scores motor composite, and mental developmental scores (mean of cognitive and language composite scores). The mean score is 100, and a score of <85 (>1 standard deviation [SD] below the mean) and ≥70 (≤2 SDs below the mean) indicates a delay and a score of <70 (>2 SDs below the mean) indicates abnormal development. Delayed neurodevelopmental outcome was defined as a score of <85 and ≥70. Abnormal neurodevelopmental outcome was defined as a score of <70 on either the PDI or the MDI of the Bayley-II or the motor composite or mental developmental score of the Bayley-III. Cerebral palsy was classified by the Gross Motor Function Classification. Patients with cerebral palsy (grades 2–5) were included in the group of infants with an abnormal outcome. No children had blindness or sensorineural hearing loss that required a hearing aid.

All cognitive tests were performed by one of two experienced psychologists.

**Enteral feeding regime**

Enteral feeding was started in all infants on their first day of life. In neonates with a birth weight of less than 1000 g, only donor human milk or mother’s milk was used in the first 4 weeks of life. A human milk fortifier was added at a feeding volume of 100 mL/kg (Prolacta +4; Prolacta Bioscience Inc., City of Industry,
CA, USA). Thereafter, mother’s milk (if available) and a bovine fortifier or infant formula were provided. In children with a birth weight between 1000 g and 1500 g, mother’s milk or donor human milk if available was used. A bovine fortifier was added at a total feeding volume of 100 mL/kg. Infants who weighed more than 1500 g received mother’s milk if available or formula and a bovine fortifier for a total feeding volume of 100 mL/kg. The total feeding volume was increased by 10 to 20 mL/kg/day depending on a physical examination of the stomach, meconium passage, and gastric residuals.

The two feeding groups were classified as any human milk (human milk with either fortifier or formula) or formula (formula only) based on feeding in the previous 24 hours before discharge from hospital. Data on feeding before discharge were retrospectively collected from the patients’ records.

Statistical analysis

Data analysis was performed with SPSS software, version 20.0, for Windows (IBM Corp., Armonk, NY, USA). Categorical data were compared using the chi-square or Fisher’s exact test. Multivariate risk profiles according to feeding strategy at discharge from hospital were computed by means of logistic regression analysis. The multivariate model was adjusted for maternal age, smoking during pregnancy, antenatal steroids, gestational age, birth weight, sex, SGA, early- and late-onset sepsis, CLD, severe IVH, PVL, ROP, and NEC between non-participants and participants. Smoking during pregnancy was significantly more prevalent in non-participants than in participants (p < 0.001), whereas surfactant was more frequently used in participants than in non-participants (p = 0.006).

Table 1 shows maternal and pre-, peri-, and neonatal data for the population of children who were born very preterm according to the feeding group at discharge from hospital.

The formula group had a significantly higher prevalence of low maternal age (< 23 years) (p = 0.001), low maternal education (< 12 years) (p = 0.032), smoking during pregnancy (p = 0.027), SGA (p = 0.002), and ROP grades 3 and 4 (p = 0.001), whereas the use of antenatal steroids was significantly lower (p = 0.005) than in the human milk group. Mean gestational age and birth weight were significantly lower in the formula group than in the human milk group (both p < 0.001). No significant differences were found regarding all other maternal and pre-, peri-, and postnatal variables between these two groups.

Results

During the study period, there were 557 live births, of which 30 children died. Of the remaining 527 children, 459 (87.1%) and 442 (83.9%) attended follow-up visits at 1 and 2 years old. There were no significant differences in maternal age, maternal education, antenatal steroid use, gestational age, birth weight, sex, SGA, early- and late-onset sepsis, CLD, severe IVH, PVL, ROP, and NEC between non-participants and participants. Smoking during pregnancy was significantly more prevalent in non-participants than in participants (p < 0.001), whereas surfactant was more frequently used in participants than in non-participants (p = 0.006).

The overall survival rate of all infants in the neonatal wards was 94.6%. Survival rates in infants who were born at 23, 24, 25, 26, 27, and 28 weeks of gestation were 20.0%, 77.8%, 78.6%, 90.9%, 90.9%, and 97.3%, respectively. The survival rates were 95.3% and 98.3% in those born at 29 and 30 weeks of gestation. All of the children who were born at 31 weeks of gestation survived. There was no significant difference in the survival rate over the 8-year study period.
Short-term morbidity

The prevalence of CLD, NEC requiring surgery, IVH grades 3 and 4, PVL, and severe ROP was 7.3%, 3.1%, 2.1%, 3.1%, and 6.2%, respectively. The overall NEC rate was 3.9%. Overall survival that was free of an adverse short-term outcome was 86.5%. The rates of adverse short-term outcomes according to the two feeding groups are shown in Table 1.

Formula feeding at discharge from hospital was related to an increased risk of adverse short-term outcome ($p = 0.002$). However, in the multivariate model after adjustment for maternal age at birth, smoking during pregnancy, antenatal steroids, gestational age at birth, birth weight, SGA, and late-onset sepsis, this significance was lost (Table 2). When we separately focused on children with different gestational ages (23–26 weeks, $n = 77$; 27–29 weeks, $n = 113$; and 30–31 weeks, $n = 337$) there was also no significant association between the feeding strategy at discharge and short-term morbidity after adjustment for the above-mentioned variables.

### Table 1. Sociodemographic and neonatal characteristics of preterm infants with a gestational age of fewer than 32 weeks according to feeding strategy at discharge from hospital

| Variable                              | Any human milk ($n = 429$), n (%) or mean ± SD | Formula ($n = 98$), n (%) or mean ± SD | p value |
|----------------------------------------|------------------------------------------------|----------------------------------------|---------|
| Maternal age < 23 years                | 28 (6.5)                                      | 17 (17.3)                              | 0.001   |
| Low educational level of the mother (< 12 years) | 162 (45.5)                                   | 47 (58.8)                              | 0.032   |
| Smoking during pregnancy               | 98 (23.0)                                     | 33 (33.7)                              | 0.027   |
| Multiple births                        | 163 (38.8)                                    | 35 (35.7)                              | 0.570   |
| Antenatal steroids                     | 389 (92.0)                                    | 80 (82.5)                              | 0.005   |
| Gestational age (weeks)                | 29.1 ± 1.9                                    | 28.2 ± 2.0                             | 0.001   |
| Birth weight (g)                       | 1304 ± 391                                    | 1032 ± 313                             | <0.001  |
| SGA                                    | 54 (12.7)                                     | 26 (26.5)                              | 0.002   |
| Male sex                               | 229 (53.4)                                    | 43 (43.9)                              | 0.089   |
| Surfactant treatment                   | 233 (55.2)                                    | 60 (61.2)                              | 0.280   |
| CLD                                    | 29 (6.8)                                      | 9 (9.2)                                | 0.421   |
| IVH (all grades)                       | 55 (13.0)                                     | 13 (13.3)                              | 0.938   |
| IVH (grades 3–4)                       | 7 (1.7)                                       | 4 (4.1)                                | 0.133   |
| PVL                                    | 14 (3.3)                                      | 2 (2.0)                                | 0.748   |
| NEC                                    | 14 (3.4)                                      | 6 (6.3)                                | 0.237   |
| ROP (grades 3–4)                       | 19 (4.6)                                      | 13 (13.3)                              | 0.001   |
| Early-onset sepsis                     | 12 (2.8)                                      | 1 (1.0)                                | 0.301   |
| Late-onset sepsis                      | 25 (5.9)                                      | 8 (8.2)                                | 0.394   |

SD: standard deviation; SGA: small for gestational age; CLD: chronic lung disease; IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity. The p values were obtained by Fisher’s exact test or the t test, as appropriate. For all variables, except for educational level of the mother, the proportion of missing data was < 5%. The proportions of missing data were as follows: 0.2% for maternal age < 23 years; 17.3% for low educational level of the mother; 0.4% for smoking during pregnancy; 1.7% for multiple births; 1.3% for antenatal steroids; 1.3% for surfactant treatment; 0.9% for CLD, IVH, and PVL; 2.8% for NEC; 2.5% for ROP; 0.8% for early-onset sepsis; and 1.3% for late-onset sepsis. There were no missing data for gestational age, birth weight, sex, and SGA.
Long-term morbidity

Neurodevelopmental outcomes at corrected ages of 1 and 2 years are shown in Tables 2, 3a, and 3b. Full assessment of motor and cognitive abilities at 1 year of corrected age was available in 459 (87.1%) of the 527 children. A total of 247 (66.0%) children in the human milk group and 57 (67.1%) in the formula group achieved normal Bayley scores in motor and mental developmental indices (range: 85–115). At this time, there were no significant differences in developmental delay (Bayley scales ≥ 70 and < 85) and abnormal development (Bayley score < 70) between the human milk and formula groups. At a corrected age of 2 years, 442 (83.9%) of the 527 children were tested. A total of 280 (77.3%) children in the human milk group and 55 (68.8%) in the formula group achieved a normal developmental outcome in motor and mental scores. There was a trend towards a better outcome at 2 years old in the human milk group compared with the formula group, but this was not significant. There were no significant
differences in long-term outcome when we separately focussed on different gestational ages (23–26 weeks, 27–29 weeks, and 30–31 weeks) between the feeding groups.

**Discussion**

The overall survival rate of all live-born infants was 94.6% in this population-based cohort of very preterm-born children between 2007 and 2014. Survival rates in the extremely preterm age group (born at < 28 weeks’ gestation) were also high at 77.8% among those born at 24 weeks of gestation, and over 90% in those with a gestational age of more than 26 weeks. Survival rates of live-born infants in population-based cohort studies greatly vary, especially regarding extremely preterm infants, 1,16–29 with rates ranging from 35% to 70%,1 and from 59% to 81% for those at 25 weeks of gestation. High overall survival rates in our children at a gestational age of 24 weeks or higher may reflect advances in perinatal and neonatal care with high rates of antenatal corticosteroids (90.2%) and surfactant use (56.3%). Our survival rate for this group is low (20%) compared with that in countries with active resuscitation for neonates born at 23 weeks of gestation (Sweden). However, during the last 3 years, we already changed our practice in favour of proactive treatment and the future survival rate of these very immature neonates will probably be higher.

The overall rate of survival that was free of an adverse short-term outcome of 82.9% for those born between 23 and 31 weeks of gestation.27 Furthermore, the prevalence of moderate/severe CLD, severe NEC, IVH, and severe ROP was 8.0%, 3.7%, 5.3%, and 1.2%, respectively. Other studies that only focussed on extremely preterm infants reported markedly higher frequencies of short-term morbidities.16,20,30 The prevalence of severe CLD in other studies ranged from 25% to 44%,20 and the prevalence of severe ROP ranged from 8% to 34%.30 The lowest prevalence of severe IVH in extremely preterm infants was 6.0% in a Swedish study,19 6.9% in a Dutch Study,16 and 5.3% in another study that included extremely preterm and very preterm infants.27 The mean incidence of NEC was reported to be 7% to 10% among extremely preterm infants.31 In the EPIPAGE-2 cohort, the rate of severe NEC was 3.7% in children born between 23 and 31 weeks of gestation.27

A total of 335 (75.8%) of 442 children showed normal motor and mental development at a corrected age of 2 years. Reported rates of no developmental impairment or disability using Bayley assessment at 2 years old in surviving infants vary from 70.6% in the Netherlands to 52.1% in Australia,32 and 42% in Sweden.18 All of these studies reported outcomes of extremely preterm infants only. The EPIPAGE-2 cohort study reported a much better outcome, where 80.5% of all children born between 23 and 31 weeks of gestation survived without neuromotor or sensory disability at 2 years of corrected age.33 However, Bayley assessment for the definition of outcome was not used in this cohort. Generally, developmental outcomes are difficult to compare because of different testing methods and different definitions of disability used.

Our study showed no difference in neurodevelopmental outcome at 1 and 2 years
of age between the human milk and formula groups as assessed with Bayley-II and Bayley-III. This result might be explained by the high breastfeeding rate of 81.4% at discharge from hospital. This finding may also be explained by the local feeding strategy using only human milk in neonates who weighed less than 1000 g and mother’s milk or donor milk if available in neonates who weighed 1000 to 1500 g. Our results are in accordance with a recently published study by O’Connor et al. These authors did not find an improved outcome in very low birth weight infants at 18 months of corrected age when supplemental donor milk instead of formula was provided as a supplement to mother’s milk. The authors concluded that if donor milk is used in settings with high provision of mother’s milk, improved neurodevelopmental outcome should not be considered a treatment goal.

The strengths of this study include the population-based cohort design with prospective enrolment of infants who were born not only extremely preterm, but also very preterm. These outcomes have been reported infrequently. Moreover, the effect of feeding during hospital stay was included in the outcome data. Specialists in paediatrics and paediatric neurology performed the follow-up examinations and certified psychologists administered the Bayley-II and Bayley-III tests.

A limitation of our study is the number of children who were lost to follow-up, although follow-up rates at 1 and 2 years of age were high at 87.1% and 83.9%, respectively. However, we found a social bias in participation, with more mothers who smoked during pregnancy refusing to participate in follow-up. Another limitation is the early age at follow-up because cognitive and academic problems may become evident later. Additionally, our study focussed on outcome differences regarding feeding strategy and was not a randomized, controlled trial. However, randomization between human milk and formula would not have been possible for ethical reasons. Moreover, only differences in outcome between those fed with any human milk and those fed with formula at discharge were calculated. This is because the precise amount of human milk could not be extracted from patients’ records retrospectively.

This study provides the first complete description of outcome of very preterm infants who were born in Tyrol. To compare these data with those of other populations, the Austrian healthcare system and policy on treatment of very preterm infants must be considered. Healthcare in Austria is accessible for all people and everyone has health insurance coverage. Perinatal care is well structured and offered to every pregnant woman. This health system may lead to better care in pregnancy and might also be an explanation for good outcome data in very preterm infants.

**Conclusions**

Our population-based study of very preterm infants shows that mortality and short-term morbidity rates are low. There is no difference in short-term morbidity or neurodevelopmental outcome at 1 or 2 years of corrected age between infants who are fed with human milk at discharge and those who are formula-fed. Advances in perinatal and neonatal care, as well as the high rate of human milk feeding during hospital stay, play an important role in a successful strategy for low rates of complications in these children.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.
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