Outcome of extremely low gestational age newborns (ELGANs) following a pro-active treatment approach

A Swiss single centre experience over 10 years

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Summary

QUESTIONS UNDER STUDY: To determine the impact of a pro-active treatment approach on outcome of extremely low gestational age neonates (ELGANs; gestational age [GA] <28 weeks) born at the perinatal centre of Lucerne, Switzerland.

METHODS: We assessed rates of survival, severe neonatal morbidity and neuro-developmental impairment (NDI) of all ELGANs born alive and treated at our centre between 2000 and 2009. The results were compared with published data from contemporary national and international cohorts.

RESULTS: Over the 10-year study period, a total of 216 ELGANs were born alive at the perinatal centre of Lucerne. The survival rate was 74% for all live-born infants, and 81% for those admitted to the neonatal intensive care unit. Among the 160 survivors, 25% sustained at least one major neonatal morbidity; severe brain injury (i.e., periventricular/intraventricular haemorrhage grade 3 or 4 and/or cystic periventricular leukomalacia) affected 10%; moderate or severe bronchopulmonary dysplasia 16%; retinopathy of prematurity ≥ stage 3 11%; and necrotising enterocolitis 2%. Neuro-developmental outcome data at 18 to 24 months was available for 92% of all survivors: 88% had no or mild NDI, whereas moderate and severe NDI were present in 10% and 2%, respectively.

CONCLUSION: When compared with published national or international data, our pro-active treatment approach to ELGANs was associated with higher or equal survival rates without increasing rates of severe neonatal morbidity or neuro-developmental impairment at the age of 18 to 24 months.

Key words: extremely low gestational age newborns; neuro-developmental impairment; pro-active treatment; provisional intensive care; survival rate; severe neonatal morbidity

Introduction

Major advances in perinatal care, such as antenatal corticosteroid (ANC) administration, surfactant replacement therapy and improved techniques for mechanical respiratory support, have led to significantly improved survival rates of extremely low gestational age neonates (ELGANs; gestational age [GA] <28 weeks) over the last three decades [1, 2]. On the other hand, the incidence of major neonatal morbidities in this population has remained unchanged [1, 3]. Concerns have been raised as to whether the increased survival rates of ELGANs would be associated with increased rates of neuro-developmental impairment (NDI) [4, 5] or not [6–10].
These uncertainties have fuelled ethical concerns regarding the best approach to ELGANs, particularly at the limit of viability (i.e., at <25 weeks of gestation). Consequently, ethical decision-making in neonatal intensive care varies widely across Europe [11]. The Swiss Society of Neonatology published its own recommendations for the care of infants born at the limit of viability in 2002 and a revised version in 2011 [12, 13]. Following the 2002 publication, survival rates of extremely preterm infants with a gestational age between 22 and 25 completed weeks increased from 31% to 40% in Switzerland without affecting the incidence of short-term morbidity. Interestingly, considerable centre-to-centre (CTC) outcome differences were noted and appeared to be unaffected by the publication of national recommendations [14]. These observations were confirmed in a ten-year-study of very low gestational age neonates (gestational age <32 weeks); in addition, risk-factor adjusted CTC differences in survival rates extended beyond the borderline viable infant population [15]. Whether these differences can be explained by unmeasured patient-level factors or whether they result from variations in the effectiveness of the care provided remains a matter of debate.

At the Children's Hospital of Lucerne, a pro-active approach to the care of ELGANs has been practiced for more than 15 years, and has been associated with significantly higher survival rates compared to the national average [15]. Generally, provisional intensive care is instituted without a priori restriction of any therapeutic options. This is followed by frequent reassessments of the potential burden and benefit for the patient. As long as the benefit appears to outweigh the burden, life-sustaining therapies are continued. On the other hand, once prognosis has become grim, redirection of care is considered and palliative care becomes a priority.

This retrospective cohort study was carried out to determine the impact of the centre's high survival rates of ELGANs on the rates of both severe neonatal morbidity and neuro-developmental impairment (NDI) at the age of 18 to 24 months. The results were compared with published data from contemporary national and international cohorts.

Patients and methods

Patient population

We assessed all infants with a gestational age between 23 0/7 and 27 6/7 weeks born alive between January 1st, 2000 and December 31st, 2009 who were admitted to the neonatal intensive care unit (NICU) of the Children's Hospital of Lucerne in Switzerland. Infants who died in the delivery room (DR) were also included regardless of whether respiratory efforts were initiated or not. Infants transferred to our centre from other level III NICUs and ELGANs with major congenital anomalies (such as genetic disorders or malformations of major organ systems) were excluded. The following perinatal data were recorded: gestational age, birth weight, ANC administration (none, incomplete: 1 dose, complete: 2 doses), singleton/multiple births, and sex. Gestational age was determined as the best obstetric estimate based on ultrasound and/or date of the last menstrual period. Gestational age was defined according to the International Classification of Disease as the postmenstrual age in weeks and days [16]. The time period between 24 weeks and 0 days and 24 weeks and 6 days, for example, is termed 24 completed weeks of gestation; the foetus has completed 24 weeks and is in the 25th week of gestation.

Rates of survival of severe neonatal morbidity

Survival rates and severe neonatal morbidities were assessed for all live-born infants as well as for those infants admitted to the NICU. The following neonatal morbidities were included: Periventricular/intraventricular haemorrhage (PIVH) was graded according to Papile et al. [17] and cystic periventricular leukomalacia (cPVL) was defined as proposed by de Vries et al. [18]. Severe brain injury was defined as the presence of either PIVH grade III or IV and/or cPVL. Severe retinopathy of prematurity (ROP) was defined as ≥ stage 3 disease using the International Committee for the Classification of Retinopathy of Prematurity [19]. Necrotising enterocolitis (NEC) was diagnosed in the presence of intestinal pneumatosis or portal venous gas and/or pneumoperitoneum (Bell's stage ≥2) [20]. Diagnosis of moderate or severe bronchopulmonary dysplasia (BPD) was based on the National Institute of Health consensus definition as a requirement for supplemental oxygen and/or mechanical respiratory support at 36 weeks postmenstrual age [21].

Neuro-developmental assessment at 18–24 months

Comprehensive neuro-developmental assessment was performed at 18 to 24 months' corrected age. Neurodevelopmental evaluation included assessment of vision impairment (blindness in one or both eyes), hearing deficit (need for corrective hearing aids in one or both ears) and abnormal muscle tone (hypotonia, hypertonia). Cerebral palsy (quadriplegia, hemiplegia, diplegia) was defined as a non-transient disorder of movement or posture, or both, causing activity limitations [22]. Developmental evaluation was performed using either the Bayley Scales of Infant Development (second edition [BSID-II], German version [23]), or the Griffiths Mental Developmental Scales (GMDS, German version [24]). Both tests are most reliable when performed at or around 24 months corrected age. The BSID-II included determination of the Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI). MDI and PDI scores of 100 ± 15 represent the mean ± 1 SD in the general population. The GMDS consists of five subscales: locomotion, personal-social, hearing-speech, eye-hand and performance. This test is designed to yield both global (sum of five subscales) and sub-scale developmental quotients (DQ) with a mean DQ ± 1 SD score for the general population of 100 ± 15 [24].

Severe NDI was defined as cerebral palsy resulting in a severely impaired mobility (PDI <55), severe cognitive impairment (MDI <55), GMDS DQ <55, bilateral blindness or deafness. Moderate NDI was defined as a PDI and/or an MDI between 55 and 69, a GMDS DQ between 55 and 69, or bilateral visual or hearing impairment. Mild NDI was defined as a PDI and/or an MDI between 70 and 84, a GMDS DQ between 70 and 84 and/or minor sensory impairments such as unilateral visual or hearing impairment. Finally, no NDI was defined as normal mobility (PDI
Neuro-developmental impairment

Neuro-developmental outcome data were available for 92% (147/160) of all surviving infants, including 13 infants with irregular follow-up (i.e., only with 12 months or after 24 months). No follow-up information was available for 13 (8%) of the survivors (fig. 1). The median BSID-II MDI was 95 (range 55–122), and the median BSID-II PDI was 92 (range 54–130). The median GMDS was 97 (range 49–116). Favourable outcome, defined as no or mild NDI, was found in 88% (129/147) of survivors assessed. Moderate NDI was present in 10%, and severe NDI was seen in 2% of the children. Survival with no or mild NDI was less frequent among ELGANs with a gestational age of 23 and 24 weeks (75 and 64%, respectively) compared with more mature infants born at 25, 26 and 27 weeks (93, 89, and 96%, respectively) (table 2).

Discussion

In this single centre cohort of 216 ELGANs, we observed an overall survival rate of 74%. Despite the fact that 25% of the 160 survivors sustained at least one severe neonatal complication, 88% had a favourable outcome when examined at 18–24 months (i.e., no or mild NDI); in contrast,
moderate and severe NDI were only observed in a minority of patients (10% and 2%, respectively).

Survival rates of ELGANs increase with advancing gestational age and, in addition, are strongly influenced by patient-level factors (birth weight, sex, single or multiple birth) and interventions (ANC, mode of delivery) that are known prior to delivery [25–27]. Several studies from the USA, Canada, Australia, and Switzerland have shown that substantial CTC outcome differences persist even after adjusting for these patient-level factors and perinatal inter-
ventions [15, 25, 28–30]. This may be due to unmeasured inherent risk factors of the patient population or, alternatively, due to differences in the treatment approach (i.e., provision of intensive care vs. primary non-intervention) or the effectiveness of the care provided.

This study reports survival rates, incidence of severe neonatal morbidity and neuro-developmental impairment at 18–24 months of age following a pro-active treatment approach to ELGANs at the Children’s Hospital of Lucerne, Switzerland. Given the wide range of national and

Table 1: Gestational age-specific characteristics of the ELGAN patient population.

<table>
<thead>
<tr>
<th>Gestational age, weeks</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>Total &lt;28 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liveborn infants</td>
<td>N = 18</td>
<td>N = 40</td>
<td>N = 48</td>
<td>N = 51</td>
<td>N = 59</td>
<td>N = 216</td>
</tr>
<tr>
<td>Median birth weight, g (range)</td>
<td>600 (390–780)</td>
<td>672 (400–880)</td>
<td>750 (460–970)</td>
<td>840 (500–1250)</td>
<td>1030 (630–1380)</td>
<td>780 (390–1380)</td>
</tr>
<tr>
<td>Male sex</td>
<td>56% (n = 10)</td>
<td>50% (n = 20)</td>
<td>42% (n = 20)</td>
<td>63% (n = 32)</td>
<td>53% (n = 31)</td>
<td>52% (n = 113)</td>
</tr>
<tr>
<td>Multiple birth infants</td>
<td>17% (n = 3)</td>
<td>10% (n = 4)</td>
<td>27% (n = 13)</td>
<td>20% (n = 10)</td>
<td>39% (n = 23)</td>
<td>25% (n = 53)</td>
</tr>
<tr>
<td>Antenatal corticosteroids (ANC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Complete course</td>
<td>17% (n = 3)</td>
<td>68% (n = 27)</td>
<td>65% (n = 31)</td>
<td>63% (n = 32)</td>
<td>66% (n = 39)</td>
<td>61% (n = 132)</td>
</tr>
<tr>
<td>– Incomplete course</td>
<td>28% (n = 5)</td>
<td>8% (n = 3)</td>
<td>15% (n = 7)</td>
<td>22% (n = 11)</td>
<td>12% (n = 7)</td>
<td>15% (n = 33)</td>
</tr>
<tr>
<td>– None</td>
<td>56% (n = 10)</td>
<td>25% (n = 10)</td>
<td>21% (n = 10)</td>
<td>16% (n = 8)</td>
<td>22% (n = 13)</td>
<td>24% (n = 51)</td>
</tr>
</tbody>
</table>

Table 2: Gestational age-specific survival, morbidity rates and rates of neuro-developmental impairment among ELGAN patient population cared for at the Children’s Hospital of Lucerne between 2000 and 2009. PIVH = periventricular/intraventricular haemorrhage; cPVL = cystic periventricular leukomalacia; BPD = bronchopulmonary dysplasia; ROP = retinopathy of prematurity; NEC = necrotising enterocolitis.

<table>
<thead>
<tr>
<th>Gestational age, weeks</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
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</tr>
</thead>
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<td>Liveborn infants</td>
<td>N = 18</td>
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<td>N = 48</td>
<td>N = 51</td>
<td>N = 59</td>
<td>N = 216</td>
</tr>
<tr>
<td>Overall survival</td>
<td>22% (n = 4)</td>
<td>55% (n = 22)</td>
<td>69% (n = 33)</td>
<td>92% (n = 47)</td>
<td>92% (n = 54)</td>
<td>74% (n = 160)</td>
</tr>
<tr>
<td>Admitted to NICU</td>
<td>N = 7</td>
<td>N = 36</td>
<td>N = 46</td>
<td>N = 51</td>
<td>N = 58</td>
<td>N = 198</td>
</tr>
<tr>
<td>NICU survival</td>
<td>57% (n = 4)</td>
<td>61% (n = 22)</td>
<td>72% (n = 33)</td>
<td>92% (n = 47)</td>
<td>93% (n = 54)</td>
<td>81% (n = 160)</td>
</tr>
<tr>
<td>Morbidity among survivors</td>
<td>N = 4</td>
<td>N = 22</td>
<td>N = 33</td>
<td>N = 47</td>
<td>N = 54</td>
<td>N = 160</td>
</tr>
<tr>
<td>PIVH ≥3</td>
<td>25% (n = 1)</td>
<td>9% (n = 2)</td>
<td>12% (n = 4)</td>
<td>6% (n = 3)</td>
<td>4% (n = 2)</td>
<td>8% (n = 12)</td>
</tr>
<tr>
<td>cPVL</td>
<td>0% (n = 0)</td>
<td>5% (n = 1)</td>
<td>3% (n = 1)</td>
<td>4% (n = 2)</td>
<td>2% (n = 1)</td>
<td>3% (n = 5)</td>
</tr>
<tr>
<td>BPD, moderate or severe</td>
<td>25% (n = 1)</td>
<td>32% (n = 7)</td>
<td>24% (n = 8)</td>
<td>13% (n = 6)</td>
<td>7% (n = 4)</td>
<td>16% (n = 26)</td>
</tr>
<tr>
<td>ROP stage ≥3</td>
<td>0% (n = 0)</td>
<td>5% (n = 1)</td>
<td>0% (n = 0)</td>
<td>2% (n = 1)</td>
<td>0% (n = 0)</td>
<td>1% (n = 2)</td>
</tr>
<tr>
<td>NEC stage ≥2</td>
<td>0% (n = 0)</td>
<td>5% (n = 1)</td>
<td>0% (n = 0)</td>
<td>4% (n = 2)</td>
<td>0% (n = 0)</td>
<td>2% (n = 3)</td>
</tr>
<tr>
<td>None</td>
<td>25% (n = 1)</td>
<td>59% (n = 13)</td>
<td>67% (n = 22)</td>
<td>79% (n = 37)</td>
<td>89% (n = 48)</td>
<td>76% (n = 121)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuro-developmental outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors assessed, % (n/N)</td>
</tr>
<tr>
<td>No impairment, % (n/N)</td>
</tr>
<tr>
<td>Mild impairment, % (n/N)</td>
</tr>
<tr>
<td>Moderate impairment, % (n/N)</td>
</tr>
<tr>
<td>Severe impairment, % (n/N)</td>
</tr>
</tbody>
</table>
international CTC outcome differences [15, 25, 28–30], centre-specific outcome information is important when counselling parents at risk of imminent extremely preterm delivery.

**Survival rates**

Compared with published data from the Swiss Minimal Neonatal Data Set (MNDS) [14, 15, 31], overall and most gestational age-specific survival rates at the Children's Hospital of Lucerne are higher. For example, Schlaphbach et al. reported survival rates of 30, 57 and 76% at 24, 25, and 26 weeks' gestation, respectively, for a Swiss national cohort born between 2000 and 2008 [31]; the corresponding survival rates for our centre are 55, 69 and 92% (table 2). The survival rates at the limit of viability in our hospital are comparable to those reported from the National Institute of Child Health and Development Neonatal Research Network (NICHD NRN) [25, 28] and the Vermont-Oxford Network (VON) [32] in the United States: these large networks reported survival rates of 55%-63% and 72–76% at 24 and 25 gestational weeks, respectively [25, 28, 32]. Finally, the EXPRESS study group from Sweden has reported excellent survival rates following a pro-active approach to extremely preterm infants born in Sweden between 2004 and 2007 [3, 33]. The survival rates of 67 and 81% at 24 and 25, respectively, exceed those observed in our study or those reported from the NICHD NRN and VON in the United States.

**Rates of severe neonatal morbidity**

Despite the fact that survival rates of ELGANs cared for at our perinatal centre are above the national average [15] the incidence of severe neonatal morbidities is not higher (i.e., major brain injury, NEC, moderate/severe BPD, severe ROP). This suggests that higher survival rates are not necessarily associated with increased rates of short-term complications (i.e., severe neonatal morbidity). Life sustaining therapies were not initiated in patients considered to have only minimal chances of survival and to be at the highest risk of severe morbidity; these patients (n = 18) died in the delivery room (fig. 1, 2). With this individualised approach, increased mortality rates are accepted in order to avoid an excessive burden of futile therapy or severe short- and long-term morbidities. This type of selection bias is likely to occur in other studies of infants born at the limit of viability. When compared with the results from the EXPRESS study group from Sweden [3, 33], rates of severe brain injury and NEC were comparable among surviving ELGANs; however, rates of moderate or severe BPD or severe ROP were lower in our cohort.

**Neuro-developmental impairment**

When compared with the results from the Swiss MNDS cohort, higher survival rates of ELGANs with a gestational age of 24 to 26 completed weeks (73 and 58% in our and the MNDS cohorts, respectively) were not associated with increased rates of NDI. In fact, we even found lower rates of impaired neuro-developmental outcome among survivors (16 and 39% for our and the MNDS cohorts, respectively) [31]. Our results are comparable to those reported by the EXPRESS study group [34].

The results of our study suggest that a pro-active treatment approach can increase the chances for survival without increasing the rates of severe neonatal morbidities and severe NDI. Active perinatal management starts before delivery, is of paramount importance in the delivery room and continues potentially for weeks in the NICU. Provisional intensive care without *a priori* restriction of any effective therapeutic options offers the opportunity to assess a preterm infant's individual response to life-sustaining therapies. It thus has the potential to more accurately predict an individual's chances for a favourable outcome. In contrast, primary non-intervention will always result in death of the ELGAN (self-fulfilling prophecy).

In our centre, a number of potentially beneficial therapeutic strategies are routinely used for ELGANs. These include – but are not restricted to – the use of lung-protective ventilation protocols [35], close monitoring of oxygen saturation targets [36], PIVH prophylaxis with indomethacin [37] (while avoiding the simultaneous use of corticosteroids [38]), initiation of gut protection on the first day of life [39], exclusive use of breast milk or donor breast milk for enteral nutrition [40, 41], and strict guidelines regarding the use of central lines. In addition, we have unrestricted access to subspecialties relevant for the care of ELGANs (e.g., cardiology, paediatric anaesthesia, paediatric surgery, radiology, paediatric neurology, etc.).

Redirection of care is only considered when complications occur that have a high likelihood of causing severe long-term morbidity with significant impact on quality of life. In contrast, severe complications that are potentially reversible are treated as vigorously as they would in more mature infants. Finally, all involved subspecialists participate in redirection of care decisions, help to fully inform parents and allow shared decision-making.

In Switzerland, recommendations for perinatal care at the limit of viability between 22 and 26 completed weeks of gestation were first published in 2002 and revised in 2011 [13]. While the new recommendations still leave room for interpretation, they are more specific regarding the suggested treatment approaches. Whether this will lead to more uniform outcomes across the Swiss centres in the next 10 years remains to be seen.

**Limitations**

There are several limitations to our study. Even though we summarised data from a recent 10-year-period, the number of patients included in each gestational age category is small. Limited sample size also prohibited analyses of temporal trends. No follow-up data was available for 8% of survivors. This rate compares favourably to other national and international studies [31, 32, 34]. Finally, assessment of neuro-development among survivors was not uniform since both BSID-II and GMDS were used, possibly limiting the comparability with other studies.

**Conclusion**

A pro-active treatment approach to ELGANs at our centre was associated with higher overall survival rates compared with those reported from a contemporary Swiss cohort. Importantly, the higher survival rates were not associated with
increased rates of severe neonatal morbidity or neuro-developmental impairment at 18 to 24 months of age. Finally, our results compared favourably with those reported from large international networks (NICHD-NRN, VON, EXPRESS study group) with comparable rates of survival, severe neonatal morbidity and neuro-developmental impairment.

References


Figure 1
ELGAN patient population cared for at the Children's Hospital of Lucerne between 2000 and 2009: DR and NICU mortality, survival and neurodevelopmental follow-up rates.

* After exclusion of one ELGAN with trisomy 21.
Figure 2
Circumstances of death in ELGANs who died in the DR.
CNS = central nervous system; TTTS = twin-to-twin transfusion syndrome. * Late termination of pregnancy.