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Trends in Mortality and Morbidity in Infants Under 500 Grams Birthweight: Observations from Our Neonatal Intensive Care Unit (NICU)

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Background: In our previous study, some changes were presented in obstetric care and we studied the morbidity and mortality trends of infants with <500 grams birth weight. Several neonatal protocol changes occurred during the study period. The aim of this study was to analyze the changes in mortality and morbidity of premature infants in light of changing neonatal protocols.

Material/Methods: We performed a retrospective study of premature infants with <500 grams birth weight, born at our department between 2006 and 2015. We divided the study period into two 5-year epochs and compared mortality and morbidity rates. We calculated the duration of mechanical ventilation and non-invasive respiratory support, and also investigated the potential impact of the differences in clinical practice.


Results: The survival rate was 30.8% during first epoch, which was significantly lower than the 70.4% survival rate during second epoch. There was no difference in the rate of complications between the 2 epochs. The total number of ventilator and non-invasive ventilation days was significantly lower in the second epoch.

Conclusions: We found significant differences in survival rates but no change in the incidence of morbidities between the 2 epochs. Therefore, although the number of neonates surviving with morbidities has increased, so did the number of those with intact survival. The increased survival of infants born with <500 grams birth weight is not associated with increased rate of morbidities. Protocol changes may have contributed to these findings; however, in a retrospective study it is not possible to separate the impact of individual changes.

MeSH Keywords: **Clinical Protocols • Infant, Extremely Premature • Survival**

Abbreviations: **BPD** – bronchopulmonary dysplasia; **CPAP** – continuous positive airway pressure; **DuoPAP** – duo-positive airway pressure; **ELBW** – extremely low birth weight; **HFNC** – high-flow nasal cannula; **HFOV** – high-frequency oscillator ventilation; **P/IVH** – peri/intraventricular hemorrhage; **NEC** – necrotizing enterocolitis; **PDA** – patent ductus arteriosus; **PROM** – premature rupture of membranes; **PVL** – periventricular leukomalacia; **ROP** – retinopathy of prematurity; **RDS** – respiratory distress syndrome; **SIMV** – synchronized intermittent mechanical ventilation; **VLBW** – very low birth weight

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Background

In the last 60 years, the viability of premature infants has improved remarkably. Papers published before the early 2000s reported high mortality rates for infants with a birth weight of less than 500 grams [1]. Reviewing the literature, we found that Seri and Evans recommended active care only to those infants whose birth weight were more than 600 grams, or more mature than 26 gestational weeks [2].

At the present time, several countries in the European Union (e.g., Ireland and Poland) define birth weight of more than 500 grams as a criterion of “live birth”. In the Czech Republic, only infants who survive the first 24 h of life count as “live births” infants.

In the past decade, numerous studies speculated about the survival rate of preterm infants with less than 500 grams birth weight, some of them reporting improvement but others reporting unchanged survival [3–8]. Neonates born at the limit of viability present serious moral and ethical dilemmas to obstetricians and neonatologists. Our department, one of the leading institutions of neonatal care in Hungary, accumulated notable experience in the treatment of these preterm infants. Hence, we believe our results may represent valuable considerations for other institutions as well.

Previously, we presented the trends in mortality and morbidity of preterm infants with a birth weight of less than 500 grams born at our institution between 2006 and 2016 [9]. We described these findings and the perinatal factors in the study period, such as maternal age, number of previous pregnancies, assisted reproduction, smoking, hypertension, PROM (premature rupture of membranes), mode of delivery, steroid prophylaxis, gestational age, birth weight, sex, 1-min and 5-min Apgar scores, and surfactant treatment. We found that gestational age, steroid prophylaxis, and caesarean section affected mortality. Preterm infants with less than 500 grams birth weight born from multiple pregnancies had higher mortality rates. PROM showed worse trends in mortality.

In the present study, we investigated mortality and morbidity rates in light of changing neonatal protocols.

Material and Methods

Our study included premature infants with less than 500 grams birth weight born between January 1, 2006 and December 31, 2015 at Semmelweis University, 1st Department of Obstetrics and Gynecology, one of the leading tertiary centers in Central Hungary. The regional referral system did not change during the study. Our department does not receive babies born outside of the hospital. In the first epoch, 39 babies (0.2%) out

of 18 952 births, in the second epoch 27 babies (0.17%) out of 15 762 births were born with a birth weight with less than 500 grams. In the first epoch, 27 out of 39 infants and 8 out of 27 infants died shortly after birth, in the first and second epoch respectively.

Protocol changes

Several changes were made in our neonatal protocols during this 10-year period. We changed the indication for and dosage of poractant alfa (Curosurf) administration. New ventilators and non-invasive ventilation equipment were installed. The indication for closure and the pharmacologic management of PDA (patent ductus arteriosus) changed as well (Figure 1).

Changes in delivery room stabilization

One of the main goals of delivery room management is to prevent newborns from losing body heat. Since 2012, we have been using plastic bags for prevention of hypothermia. In this regard, replacement of the previously-used infant warmer with a modern one (the Atom Sunflower Warmer) in 2014 was a great improvement.

Respiratory management also plays an important role in the delivery room. In 2014, replacing bag-valve-mask ventilation, a Neopuff T-Piece Resuscitator was installed, thereby refining precise pressure values during stabilization.

Changes in respiratory care

Until 2014, we maintained ventilation using the Viasys BearCub 750 and Sensor Medics HFO ventilators. Infants with satisfactory spontaneous breathing were extubated to the bubble CPAP (continuous positive airway pressure systems). From 2014, mechanical and non-invasive (DUOPAP/nCPAP/HFNC) ventilation were performed using the Acutronic Fabian, nCPAP, and Acutronic Fabian+HFO ventilators; however, 2 Sensor Medics HFO ventilators remained in use.

In the first epoch of the study, surfactant was given by early rescue protocol; infants on 40% or more O₂ received surfactant replacement. In the second epoch, we changed to prophylactic administration in ELBW (extremely low birth weight) infants.

We also changed the dosage of poractant alfa, from the previous 100 mg/kg to 200 mg/kg. If a patient required more than 30% O₂ concentration, surfactant was repeated, with a 100 mg/kg dose.

Since 2009, within the first 2 hours of life we started caffeine-citrate treatment, with a 20 mg/kg loading dose, continued with 2×5 mg/kg/day maintaining dose.

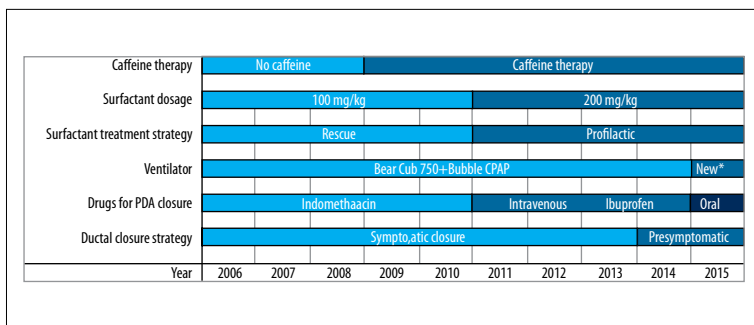


Figure 1. Protocol changes in the study period 2006–2015. *(DUOPAP/nCPAP/HFNC) Acutronic Fabian+nCPAP, Acutronic Fabian+HFOV, and Sensor Medics HFOV ventilator.

Changes in PDA closure

Until 2014, symptomatic closure was in practice at our NICU. When clinical signs were present, echocardiography was performed. Circulatory overload and left-to-right shunting without closing tendency were the criteria for pharmacological closure.

From 2014 onwards, a presymptomatic regimen was applied. We perform echocardiography on every preterm infant with less than 1000 grams birth weight at 24 h of life. If left-to-right shunting appears without contraindication, we initiate treatment.

Until 2010, indomethacin was the first-choice drug; 0.2 mg/kg, repeated twice (12 and 36 h later). From 2011 to 2014, we used intravenous ibuprofen; 10 mg/kg loading dose, followed by 5 mg/kg on 2 consecutive days. In 2015, we changed to oral administration.

Other changes

From 2012, a physiotherapist regularly treats our preterm infants and educates their parents.

Clinical data

Obstetric data was gestational age at birth, singleton/multiple gestation pregnancy, caesarean section/vaginal delivery, birth weight, sex of the newborn.

Neonatal data was antenatal steroids, Apgar scores at 1-min and 5-min, surfactant administration and dosage, duration of SIMV (synchronized intermittent mandatory ventilation), HFOV (high-frequency oscillation ventilation), and non-invasive (DUOPAP + CPAP) ventilation, caffeine treatment, echocardiography in the first week of life, pharmacologic closure of PDA, laser coagulation due to retinopathy of prematurity, surgical NEC (necrotizing enterocolitis), IVH (intraventricular hemorrhage), PVL (periventricular leukomalacia), and spontaneous fractures.

Clinically stable infants whose weight reached more than 1000 grams, tolerated feeding, and who needed no more than nasal

cannula were transferred to competent local neonatal units. These transfers usually took place before the 36th postconceptional week, so our data are not sufficient for determining BPD (bronchopulmonary dysplasia) in every case. Instead of investigating the rate of BPD, we studied the total number of ventilator and non-invasive respiratory support (nasal CPAP/DUOPAP/bubble CPAP/HFN) days.

The collected database made the multivariate analysis possible, but the number of cases restricted the applicable statistical methods. The correlation of variables was analyzed with different models. For instance, analysis of variance (ANOVA) was used if the dependent variables were dichotomous or nominal and the independent variables were continuous. In other cases, cross-table analysis was performed, analyzing distribution of parameters after their conversion from continuous to categorical variables. A difference was considered to be statistically significant if the *P* value was below 0.05.

Results

Perinatal factors in the 2 epochs: 2006–2010 vs. 2011–2015 (Table 1)

The frequency of births with birth weight less than 500 grams did not differ in the 2 groups; 0.2% vs. 0.17% (*P*: 0.46). The average gestational age at delivery, mean birth weight, male-to-female ratio, rate of multiple births (twins), antenatal steroid administration, and frequency of caesarean section was not statistically different between the 2 groups. The mean value of 1-min Apgar scores was significantly lower in the first group: 4.62 (lowest: 0, highest: 8), compared to 5.93 (lowest: 1, highest: 8) in the second group (95% CI of difference –2.317 to –0.304; *P*<0.05). The mean value of 5-min Apgar scores was significantly lower in the first group as well; 6.41 (lowest: 1, highest: 9) vs. 7.81 (lowest: 5, highest: 9) (95%CI of difference –2.233 to –0.081; *P*<0.05).

Survival rates in the 2 epochs: 2006–2010 vs. 2011–2015

During 2006–2010, out of the total 39 infants with less than 500 grams birth weight, 27 (69.2%, 95% CI: 52.4 to 83.0) died

Table 1. Perinatal Factors in the Two Epochs; 2006–2010 and 2011–2015.

	2006–2010	2011–2015	P value
Mean birth weight (gramm)	420.6 (min: 270–max: 500)	440 (min: 310–max: 500)	0.16
Mean gestational age* (week)	24.71 (min: 22, max: 29)	24.74 (min: 22, max: 30)	0.95
Female gender	76.9%	59.3%	0.12
Prophylactic steroid treatment	61.5%	66.6%	0.67
Caesarean sections	87.2%	92.6%	0.48
Twins	23.1%	22.2%	0.93
Mean Apgar 1 min	4.64 (min: 0–max: 8)	5.96 (min: 1–max: 8)	0.01
Mean Apgar 5 min	4.41 (min: 1–max: 9)	7.81 (min: 5–max: 9)	0.008

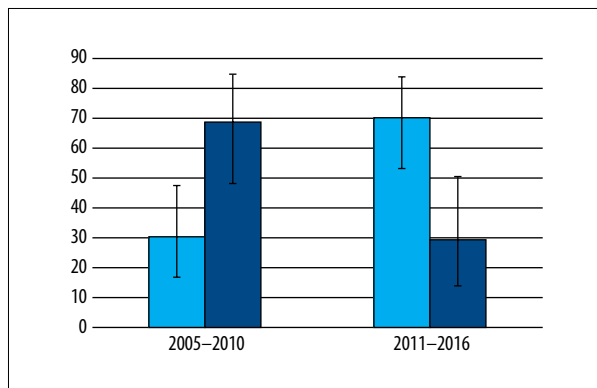


Figure 2. Survivor (light) and mortality (dark) groups.

shortly after birth and 12 (30.8%, 95% CI: 17.0 to 47.6) survived. During 2011–2015, 19 out of 27 neonates survived (70.4%, 95% CI: 49.8 to 86.3) and 8 died (29.6%, 95% CI: 13.8 to 50.2). The difference in survival rate between the 2 epochs reached statistical significance ($P < 0.05$) (Figure 2).

Changes of acute complications between 2006–2010 and 2011–2015

Duration of SIMV/HFOV ventilation was not statistically different in the 2 epochs: 44.2 ± 25.4 vs. 35.9 ± 8.7 days (95% CI of the difference: -8.18 to 24.74 ; $P > 0.05$), nor was the length of non-invasive respiratory support (DUOPAP/CPAP): 18.9 ± 19.0 days in 2006–2010 vs. 14.6 ± 10.6 days in 2011–2015 (95% CI of the difference: -8.4 to 17.2 ; $P > 0.05$).

However, total duration of respiratory support (SIMV-HFO + DUOPAP/CPAP) was significantly shorter in the second epoch: 63.1 ± 22.4 days vs. 47.8 ± 17.9 days (95% CI of the difference: 0.4 to 30.2 ; $P < 0.05$) (Figure 3).

The incidence of intraventricular hemorrhage and the incidence of periventricular leukomalacia were not statistically different in the 2 epochs. IVH occurred in 4 out of 12 infants in

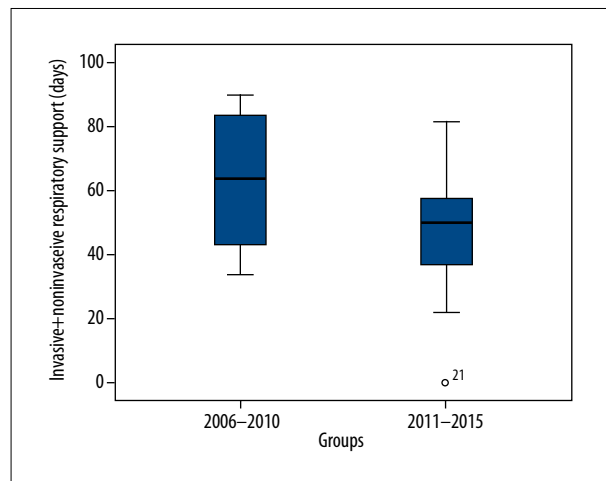


Figure 3. Total duration of invasive (SIMV and HFOV) + non-invasive (DuoPap and CPAP) ventilation.

2006–2010 (33.3%, 95% CI: 10.0 to 65.1) vs. 10 out of 19 cases (52.6%, 95% CI: 28.9 to 75.6) in 2011–2015 ($P > 0.05$). The occurrence of PVL was 1/12 (8.3%, 95% CI: 0.2 to 38.5) in 2006 vs. 3/19 (15.8%, 95% CI: 3.4 to 39.6) in 2011–2015 ($P > 0.05$).

Incidence of ROP (retinopathy of prematurity) requiring laser photocoagulation was not significantly different in the 2 groups: 8/12 (66.6%, 95% CI: 34.9 to 90.1) vs. 14/19 (73.7%, 95% CI: 48.8 to 90.6) ($P > 0.05$). Incidence of NEC requiring surgical treatment was not statistically different in the 2 epochs: 0/12 (0%) vs. 3/19 (15.7%, 95% CI: 3.4 to 39.6) ($P > 0.05$).

Spontaneous fractures during NICU stay occurred in 4 out of 12 cases (33%, 95% CI: 10.0 to 65.1) in the first epoch, while in the second epoch it occurred in 3 out of 19 infants (15.8%, 95% CI: 3.4 to 39.6), and the difference did not reach statistical significance (Figure 4).

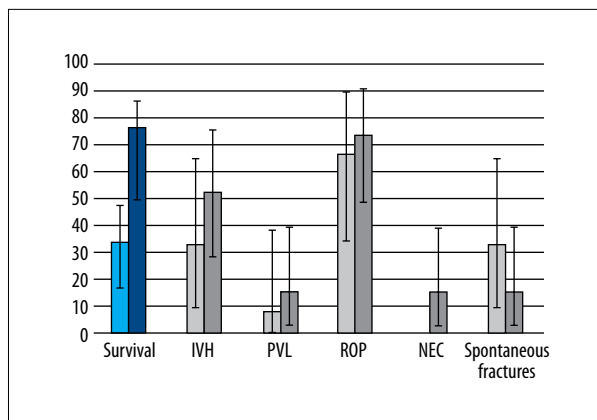


Figure 4. Survival rate (blue) and complication rate (black) of preterm born during 2006–2010 (bright) and 2011–2015 (dark).

Discussion

We found significant differences in survival rate but no change in the incidence of morbidities in preterm infants <500 grams between the 2 epochs. Therefore, although the number of neonates surviving with morbidities has increased, so did the number of those with intact survival.

Our findings represent an institution-based audit. Hence, it was not possible to draw conclusions for the whole population. It was a retrospective study and the combined action of changes makes it difficult to determine the effect of a single protocol update.

However, we were able to follow the changes in our care, which is not possible by a multi-institutional study. In addition, the number of cases was high in both epochs, compared to other published reports. Pedley et al. studied 26 preterm infants with <500 grams birth weight, in a 10 years study period [7], an Australian tertiary center studied 36 infants in a 5 years period [10]. Gillone et al. performed a population-based study with a smaller case number than our study [6]. Of course, whole population studies have large databases, e.g., Inoue et al. covered the whole Japanese population during a 10 years period [8], Lucey et al. studied 4172 infants in the Vermont-Oxford Network [1].

Reviewing the literature, we found, that our survival rates are similar to some authors' findings (more than 60%) [7,8,11], however Gillone and Upadhyay reported <30% survival rate in the <500 grams birth weight population [6,12]. Searching for the reasons behind our results, we tried to gather the protocol changes, which could contribute to the improved survival.

Changes in delivery room stabilization

Higher 1-min and 5-min Apgar scores in the second epoch presumably contributed to the better survival rates. Apgar scores

at 1 min improved due to expanded indication criteria of caesarean sections, advanced surgical techniques, and increased prevention of heat loss in preterm infants. Apgar scores at 5 min might have improved due to heat loss prevention and better resuscitator equipment. Last, but not least, continuously improving teamwork and regular staff training greatly improved our results as well.

Changes in respiratory care

However, the 2013 European protocol recommended early rescue protocol vs. prophylactic administration; we observed a strong correlation between surfactant administration and survival in our cases. This experience was the reason why we continued the early prophylactic treatment among preterm infants with less than 500 grams birth weight, despite the 2013 recommendation [13]. Since 2009, among preterm infants born under 1500 grams, we started caffeine-citrate treatment on the first day of life.

Until the end of 2014, only a small number of up-to-date ventilators with NIV modes were available at our department; therefore, until 2014 most of the infants were extubated to bubble CPAP. In our experience, many infants who otherwise required only minimal respirator settings needed reintubation because of frequent apnea. At the end of 2014, non-invasive respiratory equipment became available at our department and we were able to establish DUOPAP, CPAP, and HFNC support. From 2014 onwards, we aimed to start non-invasive respiratory support as early as possible. Based on results at other institutions, we expect these respiratory support modes will reduce the total number of respiratory days [14,15].

Changes in PDA closure and management of circulatory failure

Management of PDA among preterm infants remains controversial. In the current literature, 3 basic strategies exist: prophylactic, symptomatic, and presymptomatic treatment [16].

Until 2014, symptomatic closure was practiced in our NICU. If clinical signs were present, echocardiography was performed. Circulatory overload and left-to-right shunting without closing tendency were the criteria for pharmacological closure. Several times, pulmonary hemorrhage and severe intraventricular hemorrhage occurred before any clinical sign of PDA was present.

These acute complications prompted us to change our protocols, and from 2014 onwards a presymptomatic regimen has been used. We perform echocardiography on every preterm infant under 1000 grams birth weight at 24 h of life. If left-to-right shunting appears without contraindication, we initiate treatment. These changes resulted in higher frequency of pharmacological closure in the 2011–2015 epoch.

Until 2010, indomethacin was the first-choice drug. According to the literature, indomethacin closes the ductus arteriosus in 75% of cases [17]. Reviewing the literature, we found that both ibuprofen and indomethacin close a PDA with similar efficiency, but ibuprofen has fewer adverse effects. Hence, from 2011 to 2014 we used intravenous ibuprofen. In 2015, we switched to oral administration of ibuprofen based on the finding that both routes have the same efficacy [17].

Other changes

The cause of osteopenia among extremely low birth weight infants is multifactorial [18]. The results of enhanced physical activity and improved mineralization is not obvious in ELBW infants, and some studies reported that enhanced physical activity promoted mineralization [19].

From 2012, our department has employed a physiotherapist who regularly treats our preterm infants. We observed a trend towards reduced frequency of spontaneous fractures; however, the difference between the 2 epochs was not significant. The physiotherapist also educates parents, which in addition to the possible promotion of mineralization, increases physical bonding between parents and preterm infants.

Major complications

There was no significant difference between the 2 epochs with respect to incidence of the high incidence of BPD and intraventricular hemorrhage. The incidence of surgical NEC and periventricular leukomalacia was not significantly different between the 2 groups. In our opinion, these results are caused by the high occurrence of risk factors: prematurity, intrauterine growth restriction, and long duration of postnatal critical conditions. As compared to other authors' findings, our major complication rates are quite similar. The incidence of BPD and PVL were slightly higher [1,6,7,8,11], IVH gr. III–IV was slightly lower [1,7,12]. With the refinement of special protocols for

these critically ill preterm infants, we aim to reduce the incidence of acute complications and to improve survival.

Conclusions

There were 3 protocol updates in 2010. First, we changed from the rescue regimen to prophylactic surfactant administration. Second, we changed the initial dose of poractant alfa from 100 mg/kg to 200 mg/kg. Infants on more than 40% oxygen received a 100-mg/kg second dose. Third, infants with patent ductus arteriosus were treated with ibuprofen instead of indomethacin. Perinatal data of preterm infants did not differ between the 2 epochs, except for 1-min and 5-min Apgar scores. Based on our data, survival of preterm infants under 500 grams birth weight improved significantly to the 2010s. Changes in our protocols probably contributed to these results, but this was a retrospective study and the combined action of changes makes it difficult to determine the effect of a single protocol update.

The 500-gram weight limit, in contrast to our previous observations, does not seem to be a sharp dividing line in terms of survival. In our results, we observed a more than 50% survival rate. However, reducing the high frequency of complications (e.g., BPD, ROP, IVH, PVL, and spontaneous fractures) among surviving infants remains challenging. In the last decade, the mortality rate dropped among preterm infants with higher birth weight, and, thanks to the non-invasive respiratory trends and changes in treatment strategies of ROP, PDA, and circulatory failure, morbidity rates dropped too. We hope that use of these protocol updates for ELBW infants will lower morbidity rates of surviving infants.

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