Chapter

The Extremely Low Birth Weight Infant

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Abstract

Extremely low birth weight infants (ELBW) are defined by birth weight of less than 1000 g and are frequently born at 27 weeks' gestation (GW) or younger. The neonatologists' efforts focused on improvement of intact survival rate, especially for those born at the frontiers of viability at 22/23 GW. Survival rates of >80% for the advanced gestations and > 50% for 23–24 GW have been reported. Higher gestational age and birth weight, female gender, better maternal education, and white race have been recognized as significant predictors of decreased morbidity in ELBW infants. Although the mortality rate has significantly contracted for this group with improved technology and better understanding of pathophysiology, the proportion of surviving infants without sequelae, has not improved as noticeably. We review the short and long-term morbidities in ELBW infants and compare own and literature data. We analyze some of the specific immediate problems for this group such as: respiratory problems, infection, thermoregulation, impaired glucose homeostasis and disturbed cardiovascular and excretory functions as well as late morbidities such as bronchopulmonary dysplasia, late-onset infections, central nervous system occurrences, retinopathy and anemia of prematurity. We also deal with preventive and therapeutic strategies for improved outcome in this sensitive group of patients.

Keywords: ELBW infants, survival, morbidities, outcomes, respiratory distress, bronchopulmonary dysplasia, retinopathy of prematurity

1. Introduction

Prematurity is a significant risk factor for survival of the neonate and is related to increased perinatal mortality and morbidity. Current minimal age of viability is considered to be 22–23 weeks' gestation with dispersed reports of survival earlier than this estimated gestational age (GA) [1].

Extremely low birth weight infants (ELBW) are defined by birth weight of less than 1000 g; also, are the youngest premature newborns typically born at 27 weeks' gestation or younger [1].

Attention has turned to the improvement of the intact survival rate of extremely low birth weight infants (ELBW), particularly of those born at the boundaries of current perinatal medicine. Survival rates to hospital discharge of above 80% have been reported in Canada, USA and Japan for the 25 GW [2–4]. Developed centers report on increase survival rates also for infants born at 23–24 GW [4]

with significant variability in survival observed in resource limited centers [5, 6]. Factors found to be significantly positively correlated with improved survival and outcome of ELBW infants were: older gestational age [1, 5, 6], higher birth weight [1, 5–7], female gender [7], singleton birth [7], antenatal steroid use [1, 6–8], Apgar score at 5 min [1] and delivery by cesarean section (CS) [1, 6]. On the other hand, vaginal delivery in non-vertex presentation [1, 9, 10] placental abruption [1] and the existence of fetal growth restriction [11] have been recognized as adverse factors. Reports highlight birth weights of >750 g in association with better survival [1, 6, 12]. In our previous study, not only that we found a strong positive correlation of higher birth weights with survival, but also of broader head circumferences; the median head circumference was 2.5 cm larger for the survivors [12]. Apgar scores' median value 5 at the first minute were significantly positively associated with favorable outcome [12]. A significant correlation of caesarean section delivery with the outcome has been observed in studies [1, 6, 12], with a higher share of emergency cesarean sections in survivors [12] pointing out that CS is indeed a protective mode of delivery. However, indication of CS in pregnancies of less than 24 weeks is a matter of inclusive worldwide debate. To reach a conclusion, a nationwide survey is needed.

Although the mortality rate has significantly diminished with improved neonatal technologies, use of exogenous surfactant preparations and better understanding of pathophysiology of ELBW infants, the proportion of surviving infants without sequelae, such as chronic lung disease, cognitive delays, cerebral palsy and neurosensory deficits has not improved as noticeably [13, 14].

2. Specific problems in the ELBW infants

2.1 Thermoregulation

ELBW infants are particularly prone to heat loss immediately after birth due to high body surface area to weight ratio, thin skin, decreased brown fat tissue and decreased glycogen supply. Studies have found significant association of hypothermia to in-hospital mortality, respiratory distress syndrome, necrotizing enterocolitis (NEC), and intraventricular hemorrhage in low birth weight/preterm infants [15, 16]. A retrospective observational study performed at 29 Canadian Neonatal Networks' neonatal intensive care units encompassing 9833 infants born at <33 weeks' gestation showed U-shaped relationship between admission temperatures and adverse neonatal outcomes. Lowest rates of adverse outcomes have been associated with admission temperatures between 36.5 °C and 37.2 °C [15]. Thermal management is crucial for survival of the ELBW infants and includes interventions such as drying, heating under a radiant warmer, placing a hat on the head and plastic film over the body [16, 17]. Frequent monitoring of temperature should be done to avoid iatrogenic hyperthermia, especially when applying multiple interventions simultaneously (e.g. plastic bags + thermal mattresses) [16].

2.2 Respiratory distress syndrome

Respiratory distress syndrome (RDS) caused by surfactant deficiency is an early complication of extreme prematurity. Surfactant deficiency causes decreased pulmonary compliance, alveolar hypotension, and an imbalance between pulmonary ventilation and perfusion [17, 18]. Clinically marked by tachypnea, chest retractions, nasal flaring, cyanosis and grunting, this condition usually progresses to hypoventilation, hypoxemia and respiratory acidosis [17, 18]. RDS was recorded

in 80% of babies born at 28 weeks' gestation and in 90% of those born at 24 weeks' gestation according to Vermont Oxford Network data during 2017 [18]. Common complications of RDS comprise air leak syndromes, bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP). Animal and synthetic surfactants have been widely used for the treatment of RDS which resulted with significant reduction in mortality. Also, a shift in practice has been noted towards non-invasive ventilation techniques such as continuous positive airway pressure CPAP [19]. Recent large trials showed a lower risk of chronic lung disease or death from early stabilization on CPAP with selective surfactant administration [20]. However, infants born at 23–24 weeks' gestation, may continue to have high need for intubation during initial stabilization.

The INSURE technique (Intubate-Surfactant-Extubate) for surfactant administration involves giving surfactant through an endotracheal tube while administering positive pressure inhalations, often with premedication. This method has been used since 1994 and efficacy has been replicated in many studies [21, 22]. LISA (Less Invasive Surfactant Administration) on the other hand, is a preferred new method that involves administering surfactant via a small intratracheal catheter, with the baby breathing spontaneously on CPAP or NIPPV support, without sedation [23, 24]. However, a recent study raised concerns over relatively low success rate of the first LISA attempt, often inadequate technical performance quality and recurrent desaturations [24].

Following the increasing use of CPAP, other non-invasive ventilation methods have been subjected to research, mostly nasal intermittent positive pressure ventilation (NiPPV) [25] and high-flow nasal cannula (HFNC). Trials have failed to show difference in rates of death and BPD when NiPPV was compared to CPAP [26, 27]. HFNC has been considered as an alternative non-invasive mode for post-extubating support [28]. Current mechanical ventilation (MV) tactics include shortening of duration of MV and the use of targeted volume ventilation (VT). VT results in shorter ventilation-time, fewer air-leaks and less BPD [17].

2.3 Cardiovascular problems

2.3.1 Patent ductus arteriosus

Up to 80% of ELBW infants have a clinically significant patent ductus arteriosus (PDA). As a consequence of the left-to-right systemic to pulmonary shunting various symptoms may appear, most notably, systolic murmur, hypotension, bounding pulses, decreased urine output, pulmonary hyperemia and edema, as well as and reduced mesenteric and cerebral perfusion [29]. Contrary to term newborn who exhibit spontaneous ductus closure in 90% at 48 hours, it occurs in only 30 to 35% of infants with BW < 1000 grams during the neonatal period [29].

The diagnosis is set by echocardiography, also Doppler ultrasound of the cerebral blood vessels in search for signs of diminished perfusion. Ideal management of the PDA in premature infants is still a topic of debate, despite more than three decades of active study [29, 30]. Indomethacin was the conventional drug of choice for ductus closure, but concerns regarding its negative effects on cerebral, renal and gastrointestinal perfusion have led to investigation of other agents such as ibuprofen [30]. A 2020 Cochrane review concluded equal effectiveness of ibuprofen and indomethacin in closing a PDA. However, in the light more favorable safety profile, ibuprofen was highlighted the drug of choice with an equal effectiveness of orogastric and intravenous administration [31]. Oral paracetamol was also supported by clinical studies as equally potent drug for ductus closure [32]. Surgical ligation should only be considered in the light of failed medicaments' treatment [17].

2.3.2 Variable hemodynamics

Blood pressure (BP) of preterm newborns is marked with wide range of observed values for every GA. It is generally accepted that lower BP values are seen with decreasing gestational age and birth weight. Usually, mean arterial blood pressure corresponds to the gestational age, but this relationship is less clear for the extremely premature infants [33]. The variations in BP are related to dynamic changes in physiology during neonatal transition and various disease processes in this group of patients. It has not been proven that institution of any kind of anti-hypotensive therapy, fluid bolus or dopamine could significantly influence the rise of BP 4–24 hours after birth. Therefore, it has been suggested not to rely on a single numerical BP cutoff value for predicting infants that could benefit from anti-hypotensive treatments [33].

Recent randomized controlled trial could not show differences in hemodynamic parameters, amplitude integrated EEG variables, clinical complications or brain ultrasound findings between groups of active, moderate or permissive BP treatment of patients ≤29 GW [34]. The last composite guideline for management of neonatal respiratory distress syndrome recommends treatment of hypotension when evidenced by signs of poor tissue perfusion such as oliguria or poor capillary return, rather than treating sole numerical values [17]. Dopamine has been found more efficient than dobutamine for treatment of systemic hypotension in preterm infants, while dobutamine and epinephrine could be opted for treatment of reduced ventricular function [35]. Hydrocortisone is an alternative medicament for treatment of hypotension in extremely preterm infants [36].

Hypovolemic shock should be managed by giving non-cross-matched O-Rhesus-negative blood or alternatively by administering an isotonic crystalloid solution; the proposed dose is 10–20 mL/kg [37]. Delayed cord clamping apart from expanding blood volume, was proven in clinical studies to yield multiple potential benefits for preterm infants such as improved neurodevelopmental outcomes, reduced blood transfusions, possible autologous transfusion of stem cells, and reduced incidence of intraventricular hemorrhage [38]. However, in infants who need immediate resuscitative measures, it is recommended that placental transfusion should be discontinued [37].

2.4 Central nervous system problems

Intraventricular hemorrhage (IVH) is an extravasation of blood in the brain that originates from the subependymal germinal matrix and advances into the ventricular system, most frequently occurring in the first 3 days of life [39]. The classical grading system of the extent of cerebral bleeding includes 4 grades of hemorrhages: grade I - confined to the germinal matrix, grade II – progression to the lateral ventricle without ventricle dilatation, grade III – blood in the ventricle results in ventricular dilatation, grade IV – periventricular hemorrhagic infarction. Our study group reported an incidence of IVH in almost a third of the ELBW cohort [12]. An inverse relationship exists between the incidence and severity of IVH and gestational age; the lowermost gestations and weights are most heavily affected.

IVH has been recognized as one of the crucial morbidities in ELBW infants, with serious potential short-term sequelae in survivors such as hemorrhagic periventricular infarction, post-hemorrhagic hydrocephalus or seizures, and in the long term, developmental delay, cerebral palsy, deafness, and blindness. [40]. A shift to milder forms of neurosensory impairment has been noted reflecting better practices in perinatal care [41]. Generally, a straightforward correlation exists between the IVH grade and its prognosis. However, close neurodevelopmental follow-up is also

required for infants assigned to grades I and II IVH. Associations have been found between low-grade hemorrhages and reduced cortical volume at near term age [42]. Likewise, adverse neurodevelopmental outcomes for grades I and II IVH have been observed in follow up studies [41]. Forty four percent of ELBW children with grades III and IV intracranial hemorrhage present with disabling cerebral palsy (CP), and 45–85% of children with grade IV intracranial hemorrhage have mental retardation and CP at school age [43].

Periventricular leukomalacia (PVL) is damage to the periventricular white matter developed as a result of perinatal adverse insults such as hypoxia, hypo or hyper-perfusion, hypocarbia and chorioamnionitis combined with the defective cerebral vascular autoregulation in preterm infants. The estimated incidence of PVL is 4–15% in ELBW babies. We demonstrated an incidence of 19% in our ELBW cohort [44]. While strong correlation has been observed between diffuse cystic PVL and cerebral palsy, the clinical correlates of diffuse white mater injuries and localized cysts are not so clear-cut and might be related to a spectrum of behavioral/cognitive deficits [43].

2.5 Renal problems

Preterm infants exhibit increased sensitivity to impaired renal function. This is due to enhanced kidney maturation, fewer functional nephrons and higher renal filtration rate [45]. Acute kidney injury (AKI) in preterm infants can cause long-lasting renal damage leading to chronic kidney disease in adulthood [46]. Extremely premature infants are prone to developing AKI in the first days of life. Serum creatinine levels reflect maternal levels immediately after birth. Serum creatinine then picks, reaches a plateau in the first days of life, and declines thereafter. ELBW infants with AKI showed reduced survival until 36 weeks of post-menstrual age (PMA) [45]. Fluid status monitoring is a paramount. It involves daily monitoring of electrolytes, body weight, diuresis, blood pressure and insensible water loss.

2.6 Electrolyte imbalance

The ELBW infant is made up of 85% to 90% water, which is predominantly distributed in the extracellular space. During the first few postnatal days a weight loss of 10–20% is observed which is attributable to diuresis and can be intensified by iatrogenic causes such as radiant warmers or phototherapy. These developments in addition to the compromised renal function constitute a setting for frequent electrolyte abnormalities such as hypo/hypernatremia and hyperkalemia [47]. Disturbances of sodium are connected to the water flow and can either be presented with hypernatremia if significant amount of water is lost due to heating and phototherapy or with dilutional hyponatremia. Hyperkalemia, on the other hand, is a result of shifting from the intracellular to the extracellular compartment [47].

2.7 Impaired glucose homeostasis

Early hypoglycemia is a frequent occurrence in ELBW infants because of limited liver glycogen stores and immature endocrine mechanisms of blood glucose's control. In particular, ketogenesis and lipogenesis which lead to the production of alternative energy fuels, are limited for this group of patients, making them more dependent on glucose. Clinical conditions that are associated with hypoglycemia such as perinatal asphyxia, acidosis, sepsis and hypothermia are common [48]. Moreover, hypoglycemia in extremely preterm infants is rarely

accompanied by symptoms typical for term counterparts such as jitteriness, lethargy, apnea or poor feeding.

Hyperglycemia is also observed in extremely premature infants and in those with intrauterine growth retardation (IUGR). This condition is usually the result of excessive glucose infusion rates, drug treatment by steroids or methylxanthines, or may reflect the immaturity of the regulatory mechanisms [48].

2.8 Infection

Early-onset neonatal infection (EOI), defined as one typically occurring in the first 72 hours of life, significantly contributes to the morbidity and mortality of ELBW infants with an estimated incidence of 26 per 1000 live ELBW births in US [49]. High index of suspicion of a possible intrauterine infection should be maintained in the presence of a premature birth. Current efforts are directed toward intrapartum antimicrobial prophylaxis and early neonatal infectious screening. Early-onset infection initiates with newborn's colonization with bacteria from the maternal genital tract, most commonly group B streptococcus, *E. coli* and Listeria [49]. Also, other Gram-positive or Gram-negative bacteria, as well as fungi and viruses can contribute to the microbial spectrum of EOI.

Late-onset sepsis (LOS) results from horizontal transmission of endogenous hospital flora and typically occurs after the first week of life. Frequent nosocomial pathogens are coagulase-negative staphylococci, Klebsiella and Pseudomonas species as well as methicillin-resistant *Staphylococcus aureus* (MRSA) and fungi [50, 51]. Many institutions, including ours follow a fluconazole prophylaxis protocol for the duration of the central catheters in order to reduce catheter-associated fungaemia [51]. Our institutions' low incidence of detection of fungal sepsis (3%) among LOS is attributable to strict adherence to this Candida-prophylaxis policy [44]. Predisposing factors for late-onset infections include: immaturity of the immune system, thin permeable skin and mucous membranes, ventilator care, parenteral nutrition, central venous catheters and tubes, overcrowded nursery, inadequate hand washing routine as well as exposure to extensive handling.

Neonatal infection in ELBW infants has been associated with poor neurodevelopmental and growth outcomes in early childhood according to results of a large-cohort follow-up study [14]. Symptoms of infection in preterm newborns often include: apnea, bradycardia and cyanosis, also lethargy and increased respiratory effort, symptoms being more pronounced with Gram-negative and fungal infections than with Gram-positive ones [49]. Treatment consists of first line therapy with ampicillin and gentamycin for EOI. If the mother's vaginal swab was positive for a Gram-negative bacterium such as *E. coli*, the protocol can be revised to cefotaxime and gentamycin. Vancomycin and gentamicin are used for treating LOS and may be adjusted according to microbial sensitivity of the hemoculture. When resistant septic shock is observed ceftazidime or imipenem should be urgently added. Fluconazole or amphotericin B are given for suspected or proven fungal infections.

2.9 Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) was traditionally considered as oxygen and respirator-mediated injury related to prematurity. However, gentler ventilator techniques, prenatal corticosteroid therapy and treatment with surfactants have limited more severe lung injuries to infants of <1200 g BW and < 30 week' gestation [52]. BPD traditionally defined as a need for supplemental oxygen or ventilator support at 36 weeks' post menstrual age (PMA) occurs with an incidence of around 30% in ELBW infants [53].

In 2001, a new revised definition of BPD was devised by the National Institute of Child Health and Human Development (NICHD) categorizing the disease severity as mild, moderate, or severe based solely on oxygen dependency level at <32 GW. Mild BPD was defined by breathing room air at 36 weeks post menstrual age or discharge, moderate BPD equaled breathing <30% oxygen, and severe corresponded to breathing >30% oxygen or receiving positive pressure ventilation at PMA of 36 weeks. Radiographic findings were not included in the new definitions due to inconsistent interpretations and deficient availability at certain ages [52].

Infants with BPD were found to have higher rates of adverse neurodevelopmental outcomes and cognitive impairment in early childhood compared to those without BPD [53, 54]. At school age, children with BPD were recognized with growth impairment and academic difficulties [55]. Common rehospitalizations have been observed during the first 2 years of life, mostly as a consequence of respiratory illnesses including lower respiratory tract infections and RSV bronchiolitis [56]. RSV prophylaxis with palivizumab is included as standard care for BPD children in the first year of life.

2.10 Retinopathy of prematurity

Retinopathy of prematurity (ROP) represents interruption of the natural course of vascularization of the premature retina caused by oxygen exposure with consequent pathological compensation that results in abnormal neo-vascularization of the retina. Hence, prematurity and treatment with oxygen are the two main recognized risk factors for ROP.

Hyperoxia has been an enormous concern in the neonatal intensive care units, and the optimal oxygen saturation target ranges have been debated and explored in studies [57]. Results from several studies suggested possible harmful effect of oxygen saturation targets of 91–95%, on the contrary, lower target ranges of 85–89% resulted in increased mortality [57, 58]. Therefore, it has been recommended targeting saturations between 90 and 94% by setting alarm limits between 89 and 95%, though recognizing that ideal oxygen saturation targets are still unknown [17].

Variable incidence of retinopathy of prematurity has been reported in population-based studies due to variability in study designs and gestational ages of the included infants; reported incidences vary from 10–75% in different studies [59]. An incidence of 17.1% of severe ROP in the survivor's subcategory was reported by our group. The average number of blood transfusions for this group was 7 [44].

Severe ROP is defined by a unilateral or bilateral stage 4 or 5 disease or disease requiring laser/anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody treatment, at least unilaterally. The timing of onset of ROP depends on both the gestational and the chronological age, whereas the diseases' incidence and severity are inversely proportional to both birth weight and gestational age [59]. Apart from oxygen, suggested adverse impacts that might predispose to retinopathy of prematurity are intrauterine infection, hyperglycemia, neonatal infection, probably due to systemic inflammation, being born small for gestational age, and also repeated blood transfusions [59, 60].

Current joint recommendation of the relevant American expert societies outlines that indirect ophthalmoscopy screening for ROP should be commenced by 31 weeks PMA for infants born at 22–27 weeks and repeated in scheduled intervals thereafter. Also, all infants of <1500 g and < 30 weeks' gestation, and at-risk infants >30 weeks' gestation ought to be included in the ROP screening process [61].

Current treatment options include laser photocoagulation, intraocular injection of anti-VEGF treatment and vitrectomy. Parallel to the increased survival of the most immature infants, the number of survivors with severe ROP has also

increased. However, blindness has become a rare consequence of the most severe disease cases. Infants with ROP exhibit other ophthalmological problems such as myopia, strabismus and astigmatism [59]. Apart from visual disturbances, ROP alone or in association with other problems of the premature infants can lead to neurodevelopmental difficulties and lower academic performances [54, 55].

2.11 Anemia of prematurity

Anemia of prematurity (AOP) is a condition specific to premature infants caused by a combination of physiologic reasons such as depleted iron stores, shorter life span of erythrocytes, immature erythropoietic response, vitamin B12 and folate deficiencies as well as rapid postnatal growth, combined with iatrogenic causes observed in frequent phlebotomies for laboratory studies. Treatment of anemia consists of transfusions with erythrocyte concentrates.

Early administration of erythropoietin in the first week of life has not proven to significantly reduce the need for blood transfusions, but instead increases the risk of severe ROP [62]. Positive association has been found between anemia in the first week of life and the number of required blood transfusions with ROP development [60]. The proposed mechanism of progressing ROP is the replacement of hemoglobin F with hemoglobin A during blood transfusion which sharply increases oxygen availability to the retina [63].

Recommended transfusion thresholds are the following: hemoglobin (Hb) 12 g/dL /hematocrit (HTC) 36% for severe cardiopulmonary disease, Hb 11 g/dL /HCT 30% when dependent on oxygen and Hb 7 g/dL/HCT 25% when clinically stable beyond 2 weeks of age [17]. To decrease the risk of transfusion-related infection, a single donors' unit of packed red blood cells should be used, divided into several satellite bags to be used for the same patient for several weeks [64].

Other problems of the ELBW spectrum include: apnea of prematurity, gastrointestinal problems, feeding intolerance, hyperbilirubinemia, necrotizing enterocolitis, inguinal hernias, total parenteral nutrition-associated cholestatic jaundice as well as postnatal growth restriction [65].

3. Conclusion

The mortality rate of ELBW infants significantly diminished with improved technology and improved neonatal practices, however there are still many issues to be covered for optimal complete approach to these patients that would reduce not just the immediate, but also the long-term consequences. A multidisciplinary approach to treatment and follow up of these children is necessary, with special focus of the most sensitive areas of care such as neurodevelopmental, cognitive, auditory, visual, respiratory, speech and language, behavioral and emotional. Providing a family-centered care and structuring of appropriate data basis is necessary.

Conflict of interest

The authors declare no conflict of interest.

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