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ON THE LIMIT OF VIABILITY
Extremely Low Gestational Age at Birth

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SUMMARY

Background: Survival is not an adequate measure of success when managing preterm infants < 24 weeks gestational age (GA).

Objective: To evaluate neonatal morbidity, survival rate and outcome of preterm infants < 24 weeks GA at birth, in our Neonatal Intensive Care Unit.

Material and methods: Retrospective chart review, 1996-2009. Collected data included neonatal morbidity and mortality, follow-up at the outpatient department regarding to medical problems and neurodevelopmental and behavioural outcomes.

Results: 53 preterm neonates (27 male/ 26 female) were included; weight at birth: 630g (360-870); gestational age: 23.5 wks (22-24); outborn: 9 (17%); any antenatal steroid: 57%. Neonatal morbidity included: hypotension 68%; respiratory distress syndrome: 98%; pneumothorax: 11%; patent ductus arteriosus: 42%; noso sepsis: 72%; necrotizing enterocolitis (>2A): 54%; intraventricular hemorrhage (III+IV): 34%; retinopathy of prematurity (>2): 20%; bronchopulmonary dysplasia: 71%. Mortality rate was 87% (n=46). Antenatal steroids rate was 71% and 54%, for survivors and deceased newborns, respectively. Out of the seven (13% of total) survivors aged between 7 months and 14 years old (two under 24 months), five (71%) present major sequelae at the follow-up, while two (29%) exhibit normal "border line" development.

Conclusions: Based on these findings it seems that other characteristics of the infants and pregnancies, and not gestational age alone, should be considered before a decision is taken.

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RESUMO

Recém-Nascido de Extremamente Baixa Idade Gestacional ao Nascimento

Introdução: A sobrevivência não é uma medida adequada de sucesso no tratamento do recém-nascido pré-termo <24 semanas de idade gestacional (IG).

Objetivo: Avaliar a morbidade neonatal, taxa de sobrevivência e evolução de recém-nascidos pré-termo <24 semanas IG ao nascer, na nossa Unidade de Cuidados Intensivos Neonatais.

Material e métodos: Estudo retrospectivo, 1996-2009. Foram colhidos dados em relação a morbidade e mortalidade neonatal, seguimento no ambulatório incluindo problemas de saúde, do desenvolvimento neurológico e alterações comportamentais.

Resultados: 53 recém-nascidos pré-termo (masculino 27 / feminino 26) foram incluídos, peso ao nascer: 630g (360-870), idade gestacional: 23,5 semanas (22-24); admitidos do exterior: 9 (17%); corticoesteróide pré-natal: 57 %. A morbilidade neonatal foi: hipotensão 68%, síndrome da dificuldade respiratória: 98%; pneumotórax: 11%; persistência do canal arterial: 42%; sépsis nosocomial: 72%, enterocolite necrosante (> 2 A): 54%, hemorragia intraventricular (III + IV) : 34%; retinopatia da prematuridade (> 2): 20%; displasia broncopulmonar: 71%. A taxa de mortalidade foi de 87% (n = 46). A taxa de corticoesteróides pré-natal foi de 71% e 54%, para os sobreviventes e falecidos, respectivamente. Dos sete sobreviventes (13% do total) com idades entre 7 meses e 14

anos (dois < 24 meses), cinco (71%) apresentam sequelas graves no seguimento, enquanto dois (29%) apresentam desenvolvimento no limite do normal.
Conclusões: Baseado nestes resultados, parece que outras características das crianças e gestação, e não apenas a idade gestacional, devem ser considerados antes de tomar uma decisão em relação à reanimação e investimento.

INTRODUCTION

Advances in perinatal practices and technologies have resulted in decreasing mortality rates for preterm infants. The mortality rates of extremely low birth weight infants demonstrated definitive improvement. [1,2] In Portugal, data from the National Network of the Very Low Birth Weight Infant also demonstrates improvement in survival of extremely low gestational age (GA) preterm neonate. [3] A total of 12,826 very low birth weight infants born from 1 January 1994 to 31 December 2008 were included in the National Portuguese Network of the Very Low birth Weight Infant, with a prevalence of 0.66%-0.99% of all live born. The global mortality was 11%. The major improvement in survival was in the babies more than 1000 g. Since 2004, the threshold of viability is 25 weeks, but the intact survival is around 28 weeks. In the last 10 years, with more efficient regionalization, more very low birth weight babies are born in the right place. After reinforcement of regionalization policies, we found improvements in mortality for very low birth weight infants at all GA, including those of 23 and 24 weeks. The reform of perinatal care in Portugal is an example of how a good diagnosis and adequate proposals combined with a strong political will is crucial for changing. [3]

Survival may not be an adequate measure of success when treating preterm infants ≤ 24 weeks of GA. There is evidence of sustained adverse neurodevelopmental and behavioural outcomes at this extremely low GA. [4,5] There are also recent studies suggesting that adult performance of preterm infants that had several school problems are not different from their term counterparts and other reports that even preterm infants with major sequelae and their family rate their lives as valuable when quality of life is assessed by different tools. [6]

Although in Portugal a "do not resuscitate" order (comfort care alone) is proposed for newborns with a GA < 24 weeks at birth, since 2004, by the National Society of Neonatology, [7] some centers still resuscitate preterm neonates of 22 and 23 weeks GA. It is important for each neonatal intensive care unit (NICU) to know and to chare its own results, in order to better inform parents about prognosis and to allow creating a consensus that can help in decision-making.

The aim of this study was to evaluate survival rate, neonatal morbidity, and outcome of survivors after our NICU discharge, of preterm infants ≤ 24 weeks GA.

MATERIAL AND METHODS

A retrospective chart review of the preterm infants ≤ 24 weeks (24 weeks and 6 days inclusive) GA admitted over the last fourteen years (1996 - 2009) was performed. Data collected included perinatal care, neonatal morbidity and mortality, and follow-up at the outpatient department of the survivors regarding, especially, to neurodevelopmental and behavioural outcomes.

Our center is a level III NICU from a Pediatric Service of a university hospital, with an average of 3,000 live births per year. The Service of Pediatrics includes Pediatric Surgery, Pediatric Cardiology and Cardiothoracic Surgery. Our NICU admits about 500 newborns per year, including an average of 50 very low birth weight infants. Our clinical practices, equipment and staff did not change significantly over the last fifteen years, except for an increase in early nasal CPAP (continuous positive airway pressure) use and volume guarantee as ventilatory strategy for very low birth weight infants. The unit has nine intensive care posts and is equipped with the same ventilators (Babylog 8000 plus, VipBird, Avea, Infantflow CPAP), including high frequency oscillatory ventilation (Sensor Medics 3100A), since 1996.

As rule at our institution, obstetricians call the neonatologist for all births at GA 22 - 24 weeks. We resuscitate all 23 and 24 weeks GA preterm infants, independently of other factors such as gender, antenatal steroids, multiple birth, or parents wish. Those preterm neonates of 22 weeks are only resuscitated if they show evidence of viability, if there is doubt on datation of pregnancy or according to parents wish. The inborn preterm newborns included in this study were all the preterm newborns with GA 22-24 GA weeks born during the study period. They were all born alive, and resuscitated in the delivery room. Care was given until death in all cases, as police in our NICU.

GA was assessed by menstrual age (women with regular menstrual cycles), ultrasound examination (when a discrepancy of two or more weeks existed between the age derived by menstrual dating and the age derived sonographically, or in the absence of a menstrual date) [8] or the New Ballard Score (in the absence of obstetrical indexes). [9] Intrauterine growth restriction was defined as

a birth weight below 10th centile of Fenton`s fetal growth charts. [10]

Antenatal steroid regimen was performed with dexamethasone (total dose of 24 mg, divided into two doses given intramuscularly every 12 hours) until 2003, and with betamethasone (24 mg, divided into two doses given intramuscularly 24 hours apart) thereafter, in pregnancies with threatened preterm labour. We considered that there was antenatal steroid treatment when at least one dose was administered to the mother before delivery.

Hypotension was defined as a mean arterial blood pressure over two standard deviations below normal for age, based on values from Hegyi T et al. [11] The method of measurement was a cuff connected to a monitor Hewlett Packard (Omni Care 71034, Boeblingen, Germany). When doubt exists, arterial blood pressure is simultaneously measured in a Dinamap™ XL vital signs monitor (New York, USA), with cuff (from Jonhsons and Jonhsons Medical Inc, USA).

Respiratory distress syndrome (RDS) was defined according to the following criteria: a requirement for supplemental oxygen to maintain PaO_2 > 50 mmHg, or a requirement for supplemental oxygen to maintain a pulse oxymeter saturation over 85% within the first 24 hours of life and; (2) a chest radiograph consistent with RDS (reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) within the first 24 hours of life.

Hemodynamically significant patent ductus arteriosus (PDA) was diagnosed on the basis of the echocardiographic findings. Our police is that the first evaluation is usually performed between 24 and 72 hours of life, with daily evaluation until closure of the ductus. Echocardiographic criteria for treatment are: a ductal diameter > 1.4 mm; a relation left atrium/ aortic root > 1.3: 1; and a retrograde diastolic flow in descending aorta > 30% of the anterograde flow. The standard treatment was indomethacin.

Early neonatal sepsis was considered when biological markers (positive reactive C protein, thrombocytopenia, elevation or a decrease in with blood cell count) of infection and/or a positive blood culture were present in the first 72 hours of life. Nosocomial sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture, after 72 hours of life.

The criteria of Bell were used for the diagnosis and staging of necrotizing enterocolitis (NEC). [12] Staging of retinopathy of prematurity (ROP) was done according to the International Classification. [13,14] Intraventricular hemorrhage (IVH) was classified according to Papile LA. [15] Periventicular leukomalacia (PVL) was classified according to de Vries L and Rennie JM. [16]

Table 1 – Neonatal morbidity (n=53)

morbidity	n (%)
Hypotension inotropic support	36 (68) 32 (60)
Respiratory distress syndrome surfactant	52 (98) 52 (98)
Pneumothorax	6 (11)
FiO_2 > 0.21	53 (100)
ET and mechanical ventilation	53 (100)
Patent ductus arteriosus indomethacin	22 (41.5) 18 (33.9)
Early sepsis Nosocomial sepsis	6 (11.3) 21 (72.4)*
Necrotizing enterocolitis (NEC) (≥ 2 A) NEC surgery	13 (54.1)† 5 (20.8)
Intraventricular hemorrage (grades III-IV)	18 (33.9)
Periventricular leukomalacia	8 (15)
Retinopathy of prematurity (ROP) (> 2) ROP surgery	3 (20)§ 2 (13.3)
Bronchopulmonary dysplasia (O_2 at 36 weeks)	5 (71.4) g

ET – endotracheal tube; * 29 neonates alive after 72 hours of life; † 24 neonates alive after day 7 of life; § 15 neonates alive at day 28 of life;g 7 neonates alive at 36 weeks post-conceptional age

Table 2 – Causes of death (n=46)

In the first week of life (n=29)
Extreme immaturity = 13
Respiratory distress syndrome = 4
Respiratory distress syndrome + intraventricular hemorrhage IV = 4
Congenital pneumonia = 3 (confirmed at autopsy)
Intraventricular hemorrhage IV = 3
Meconium aspiration = 2 (confirmed at autopsy)
After the first week of life (n=17)
Sepsis = 4
Intraventricular hemorrhage IV = 3
Necrotizing enterocolitis = 3
Extreme immaturity = 1
Intraventricular hemorrhage IV + necrotizing enterocolitis + sepsis = 1
Intraventricular hemorrhage IV + sepsis = 1
Necrotizing enterocolitis + patent ductus arteriosus + sepsis + acute renal failure = 1
Necrotizing enterocolitis + sepsis =1
Sepsis + pneumonia + intraventricular hemorrhage IV + periventricular leukomalacia =1
Pneumonia = 1 (confirmed at autopsy)

The diagnosis of bronchopulmonary dysplasia (BPD) was made if the infant was chronically oxygen dependent at 36 weeks of corrected age, and had a characteristic chest radiograph. [17]

Histological chorioamnionitis was classified according to the method proposed by Blanc.[18] All grades of histological chorioamnionitis were considered together.

Autopsy study of the deceased infants was consented in 15 cases, and data were used to complete clinical data. Neurodevelopmental sequelae at the follow up were classified in mild, moderate and severe. [19] The follow-up after discharge, at the out-patient department, is performed by a multidisciplinary team, including neonatology/ pediatrics, ophthalmology, audiology, neurology, developmental assessment, psicology, psychiatric support, physiotherapy, nutrition, and if needed, pediatric surgery, gastroenterology and pediatric cardiology. The development is usually assessed once a year using the Griffiths scale (until eight years old).

RESULTS

A total of 53 preterm neonates were admitted during the study period, 27 (51%) males, 26 (49%) females, with a median birthweight (BW) of 630 g (360 – 870) and a median GA of 23.5 weeks (22–24). Three (5.6%) were classified as intra-uterine growth restriction. Antenatal steroids (any dose) were used in 30 (56.6) neonates. Two (3.7%) preterm neonates were 22 weeks GA at birth, 23 (43.3%) were 23 weeks, and 28 (52.8%) were 24 weeks. Forty four (83%) neonates were inborn, and represent all the preterm newborns ≤ 24 GA born in our maternity during the study period. Nine (17%) were outborn patients that were referred to our institution because of NEC (n=6) and preterm birth (n=3). All neonates were intubated in the delivery room and started on mechanical ventilation. The neonatal morbidity is reported in table 1. Fifteen (28%) preterm neonates were alive by 28 days of life and seven (13%) by 36 weeks of post-menstrual age.

A total of 46 (86.7%) neonates were deceased [median: day 2 of life (1-70)]. Death occurred in the first day of life in 19 (36%) newborns; in day 2 of life in five (9%); from day 2 to day 7 in five (9%); and after day seven in 17 (32%). The causes of death are reported in table 2. Overall survival rate was 13.3%. Survival at 22 weeks GA was 0% (0/2); at 23 weeks was 13% (3/23); and at 24 weeks was 14.2% (4/28) Deceased neonates were lighter and had a lower rate of antenatal steroids use than survivors, table 3.

At the follow-up analysis, two patients were less than 18 months of life (short term follow-up), and one did not present any evident major sequelae; five patients were more than two years old, and one did not present any major sequelae, Table 4.

DISCUSSION

The limit of viability is given by a survival over 50%. In Portugal, this limit is on 25 weeks GA at birth. For this reason, the group of preterm neonates born before

Table 3 – Demographics of deceased versus survivors.

Characteristic	Deceased (n=46)	Survivors (n=7)	p
Birtweight (g) median (min-max)	620 (360-835)	650 (580-870)	0.03 §
Gestational age (weeks) median (min – max)	24 (22-24)	24 (23-24)	ns §
Antenatal steroids n (%)	25 (54)	5 (71)	0.001*
Histological chorioamnionitis n (%)	35 (76)	3 (43)	ns *
Gender M (%) / F (%)	23 (50) / 23 (50)	4 (57) / 3 (43)	ns ‡

§ – Mann-Whitney test; * - Pearson Chi-Squared test; ‡ - Fischer´s exact test; ns – not significant

25 weeks GA is the one of higher risk for neurological sequelae. [20] The resuscitation of these preterm infants presents complex medical, social and ethical issues for the families and health professionals.

In Portugal the mortality rate of preterm infants ≤ 24 weeks GA (22, 23 and 24 weeks GA) was 71% in 2005 and has decreased to 63.7% in 2009 (unpublished data from the National Network of the Very Low Birth Weight Infant). This is a high rate of mortality and there are no data on neurodevelopmental outcome of the survivors. Anyway, the increase in survival rates associated to technological development of perinatal medicine does not seem to be followed by a decrease of neurological sequelae.[21-26] We also know that there are variations in survival rates to discharge from NICUs for very preterm deliveries across regions.[27] Presumably, there are also differences on short and long term neurodevelopmental outcomes across regions, and these data should be disclosed.

For these infants born in the "gray zone" [28] of viability, the line between patient autonomy and medical futility is blurred, and medical decision-making becomes even more complex and needs to embrace careful consideration of several factors. These factors include appraisal of prenatal data and the information obtained during consultations with the parents before delivery, the most accurate evaluation of the patient`s GA, birthweight and clinical condition upon delivery, ongoing reassessment of the patient`s response to resuscitation and intensive care and continued involvement of the parents in the decision-making process after delivery.

In this study, all patients were submitted to intubation after birth and started on mechanical ventilation. Death in the first days of life occurred in a significant proportion of neonates, and this may indicate that these deceased neonates probably should have not been resuscitated in the delivery room. Clinicians may not be acting in the best interest of the baby, although we know that they are doing their best. To which extent their best is the best for the baby, this is an unanswered question.

In this series, a high morbidity rate including a high prevalence of intraventricular hemorrhage and periventricular leukomalacia was observed. The majority of neonates with severe intraventricular hemorrhage were deceased, nevertheless three survivors are severely affected. Also, a significant number of preterm neonates that did not die in the first days of life, presented an ominous clinical course and came to death before the 36 weeks of post-conceptional age.

Our results are worse than some other reports, and may be that other characteristics of the infants and pregnancies should be considered before a decision is taken. One of these is the use of antenatal steroids, that was significantly lower in the deceased preterm newborns. The occurrence of histological chorioamnionitis was higher in the deceased group of children, although the difference was not significant.

This study, is limited for the small number of cases, but reveals a non enthusiastic outcome for survivors at the threshold of viability. Although two (28.5%) of the survivors present a neurodevelopment near the normal range, one of them was less than 18 months age at the last clinical evaluation, and this is a very short term follow-up. A longer follow up will probably reveal important neurological sequelae, once the child is affected by severe bilateral intraventricular hemorrhage and cystic periventricular leukomalacia.

Our series is also limited because it reflects the perinatal care of one single institution. Based on our results it seems that it is not worthwhile to pursue aggressive support of infants born at ≤ 24 weeks GA. Nevertheless, according to literature and results from other centers, may be infants of 22 weeks should not be resuscitated and infants of 24 weeks must be resuscitated.

There is a great need of longitudinal studies including large numbers of preterm neonates ≤ 24 weeks GA in order to substantiate our knowledge on neurodevelopmental, behavioural and other clinical problems to help clinicians and parents in the decision making process.

Table 4 – Sequelae at follow-up.

Patient	Year of birth	Neonatal morbidity	Sequelae at follow up
Male BW=870g GA=23weeks antenatal steroids	1996	RDS, MV=37 days, oxygen 84 days, sepsis noso, ROP 1	**Severe** low IQ epilepsy **Moderate** hyperactivity anxiety impulsive and not adequate responses **Mild** stamming
Female BW=810g GA=24 weeks antenatal steroids	1996	RDS, MV=77 days oxygen 160 days (BPD) pneumothorax PDA, indomethacin Sepsis noso IVH-I ROP 3	BPD, oxygen until 19 months of life, multiple admissions for respiratory infections in childhood neurological: no sequelae, development "border line"
Male BW=806g GA=23 weeks antenatal steroids	2002	RDS, MV=78 days oxygen 100 days (BPD) sepsis noso HIV-III	**Mild** mild developmental delay squint and refractory defect
Male BW=610g GA=23 weeks antenatal steroids	2005	RDS, MV=85 days oxygen 98 days (BPD) PDA, surgical closure of PDA Sepsis noso NEC≥2 A cystic LPV	**Severe** bilateral deafness developmental delay **Mild** spastic diplegy
Female BW=630g GA=24 weeks antenatal steroids	2008	RDS, MV=75 days oxygen 65 days PDA, surgical closure of PDA sepsis noso NEC IIIB IVH-III	short bowel syndrome after large bowel resection secondary to NEC, multiple respiratory infections **Severe** developmental delay
Male BW=650g GA=24 weeks no antenatal steroids	2009	RDS, MV=30 days oxygen 87 days (BPD) PDA, indomethacin IVH-IV / IVH-III cystic PVL ROP 3	"apparent" normal development at 7 months age (short term follow up)
Female BW=530g GA=24 weeks antenatal steroids	2009	RDS, MV=35 days oxygen 87 days (BPD) sepsis noso NEC IIIB cystic PVL ROP 3	**Severe** bilateral visual impairment, E>D (short term follow up)

BW – birthweight; GA – gestational age; IQ – intelectual quotient; IVH – intraventricular hemorrhage; LPV – leukomalacia periventricular; MV – invasive mechanical ventilation; NEC – necrotizing enterocolitis; PDA – patent ductus arteriosus; RDS – respiratory distress syndrome; ROP – retinopathy of prematurity

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