Original Paper

Neonatology

Neonatology 2017;111:234–239
DOI: 10.1159/000452195

Received: April 5, 2016
Accepted after revision: October 3, 2016
Published online: November 29, 2016

End-of-Life Care and Survival without Major Brain Damage in Newborns at the Limit of Viability

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Keywords
Brain damage · End-of-life care · Prematurity · Morbidity · Mortality · Limits of viability · Clinical decision-making

Abstract
Background: The probabilities of survival and survival without major brain damage (MBD) are low in newborns at the limit of viability. Survival without MBD constitutes a major concern for parents and professionals. ***Objectives:*** To know the probabilities of survival without MBD in newborns ≤26 weeks' gestational age (GA) relative to the total number of survivors, whether these probabilities vary with GA, and how end-of-life (EoL) decisions influence these results. ***Methods:*** We included all live-inborn patients of 22–26 weeks' GA, without major congenital anomalies, born in collaborating centers of the Spanish SEN1500 Network (2004–2010). MBD was defined as the presence of severe intraventricular hemorrhage and/or periventricular leukomalacia. ***Results:*** A total of 3,371 patients were born alive, 3,236 of whom were admitted to the neonatal intensive care unit (NICU). Survival without MBD was 44.4% among patients admitted to the NICU, increasing from 12.5% at 22 weeks to 57.9% at 26 weeks' GA. The proportion of survivors without MBD relative to the total number of survivors was 81.1%, and it was independent of GA. EoL decisions preceded one-third of all deaths and were more frequent among the most immature patients. ***Conclusions:*** The proportion of survivors without MBD, when referred to the total number of survivors, is relatively high and is independent of GA. EoL decisions after the occurrence of MBD seem to play an important role in this respect. These results support the attitude of "giving an opportunity" even to the most immature patients, if this is in accordance with the parents' wishes.

Introduction

Advances in perinatal medicine during the last few decades have resulted in the survival of increasingly more immature patients. It is a well-known fact that, at the limit of viability, the probabilities of survival and survival without major morbidity increase with each additional week of gestational age (GA) [1–10]. However, some studies have found no or only modest change over time in the proportion of survivors affected by major neonatal morbidity [8, 10]. In addition, due to financial issues,

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concerns about patient outcomes, and difficulties with outcome prediction, controversy persists regarding the intensity and appropriateness of neonatal medical treatment [11, 12]. There is a range of options to be considered for the perinatal care of extremely preterm infants. Palliative and comfort care can be offered for patients considered nonviable. At the other end of the spectrum, when the primary focus is survival, full resuscitation measures and intensive therapy can be provided. An important drawback of this course of action is the difficulty in predicting patient outcomes.

For many parents and clinicians, the worst-case scenario is not considered to be death but rather survival with severe disability. In these cases, a criterion for intervention is the probability of survival without major brain damage (MBD) diagnosed during the neonatal period. This probability is usually calculated as the proportion of survivors without major neurological morbidity to all live births. This proportion is very low in extremely premature neonates; nevertheless, some parents and professionals may feel better "giving a chance" to the newborn. In this situation, consideration of survival without MBD among all survivors, instead of among all live births, may be more useful in the decision-making process [12].

The aim of our study was to determine the probabilities of survival and survival without MBD in newborns ≤26 weeks' GA relative to both the total number of patients admitted to the neonatal intensive care unit (NICU) and the total number of survivors. We also wanted to know whether these probabilities varied with GA, analyze possible underlying causal factors, and determine the potential implications for clinical practice.

Patients and Methods

This is a subanalysis of a population of extremely preterm infants from the Spanish SEN1500 Network, previously described [13]. This database systematically collects and analyzes data on very-low-birth-weight infants born in or admitted to the NICU of participating centers. Its characteristics, quality control, and data confidentiality system have been described elsewhere [14], and the protocol for data collection and processing was previously approved by the institutional review board of each hospital.

For the purpose of this study, we included all live-inborn patients ≤26 weeks' GA without major congenital anomalies who were cared for in the participating centers from 2004 to 2010. Live births were defined as newborns who showed any signs of life (a heartbeat, breathing efforts, spontaneous muscle movements). Outborn patients were excluded to avoid potential selection bias and to exclude possible morbidity directly related to patient transfer. The GA was estimated in completed weeks according to the last menstrual period, obstetric parameters, and/or an early prenatal ultrasound. When needed, a neonatologist estimated the GA based on physical examination of the newborn.

Mortality was defined as a patient's death before hospital discharge, and end-of-life (EoL) decisions referred to medical decisions that hastened death. Withholding care described the absence of further escalation of care (e.g., intubation or cardiopulmonary resuscitation), and withdrawal of treatment was the discontinuation of ventilatory support and/or inotropes. MBD was defined as the presence of severe germinal matrix-intraventricular hemorrhage (GM-IVH) (grades 3 and 4 of Papile et al. [15]) and/or periventricular leukomalacia (cysts or persistent periventricular echogenicities for more than 14 days) on cerebral ultrasound (CUS). CUS were carried out at the discretion of the attending neonatologists at each center but included at least 3 studies at specific time periods, i.e., in the first week of life, at around 28 days of age, and at discharge.

Statistical Analysis

We used SPSS-20 software (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as means and SD or medians and IQR, and comparisons between groups were performed with the Student *t* test or the Mann-Whitney *U* test, as appropriate, or ANOVA or Kruskal-Wallis tests for comparisons between more than 2 groups. All of the hypotheses were 2-tail tested, and $p < 0.05$ was considered statistically significant.

Results

According to the National Institute of Statistics, 28,102 very-low-birth-weight infants were born in Spain during the study period, 19,482 (69.3%) of whom were registered in the SEN1500 Network. Of these, 3,371 infants ≤26 weeks' GA were born alive without severe congenital anomalies. A total of 135 neonates (4%) died in the delivery suite. The remaining 3,236 patients were actively resuscitated and admitted to the NICU. Patients who died in the delivery room were on average more immature, were less likely to have received antenatal steroids, were born less frequently by C-section, and had lower Apgar scores (Table 1). The decision to withhold or withdraw therapy was more frequent in this group than in patients who were admitted to the NICU. The distribution of live born patients by GA and the proportion of them who died in the delivery room and who were admitted to the NICU, together with the main results regarding survival, are summarized in Table 2. Out of 3,236 admitted patients, 1,796 (55.5%) survived and were discharged from the hospital. Of those, 1,742 had reliable data from CUS performed before hospital discharge. The rates of survival and survival without MBD relative to the total number of patients admitted to the NICU increased significantly with increasing GA. However, the proportion of survivors without MBD relative to the total number of survi-

Table 1. Comparison between patients admitted to the NICU and those who died in the DR

Variable	Admitted to the NICU (n = 3,236)	Died in the DR (n = 135)	p
Assisted reproduction technologies	16.5	16.8	0.936
Prenatal care	86.5	90.5	0.172
Antenatal steroids	82.6	43.8	<0.001
Multiples	29.2	33.3	0.295
Male sex	55.2	63.1	0.065
C-section	47.0	22.0	<0.001
Gestational age, weeks	25.1±0.9	23.4±1.0	<0.001
Birth weight, g	774.0±156	580.6±123	<0.001
Apgar score ≤3			
First minute	26.7	99.3	<0.001
Five minutes	5.3	96.2	<0.001
Resuscitative effort[1]	100	32.6	<0.001
Withholding or withdrawing therapy	36.9	88.0	<0.001

Values are percents, or means ± SD, unless otherwise specified. DR, delivery room. [1] Includes all attempts at stabilization with drying, physical stimulation, secretion suctioning, noninvasive ventilation, intubation, cardiac compression, and/or epinephrine administration, when indicated.

Table 2. Distribution of patients by GA, and results

GA, weeks	22	23	24	25	26	Total
Total live births, n	30	260	727	1,044	1,310	3,371
Died in the delivery room, n (%)	22 (73.3)	61 (23.5)	33 (4.5)	15 (1.4)	4 (0.3)	135 (4.0)
Admitted to the NICU, n (%)	8 (26.7)	199 (76.5)	694 (95.5)	1,029 (98,6)	1,306 (99.7)	3,236 (96.0)
Total survivors, n	1	26	256	573	940	1,796
Percent of total live births	3.3	10	35.2	54.9	71.7	53.3
Percent of patients admitted to the NICU	12.5	13.1	39.9	55.7	72.0	55.5
Survivors without MBD, n/N	1/8	19/198	196/689	460/1,014	737/1,273	1,413/3,182
Percent of patients admitted to the NICU	12.5	9.6	28.4	45.4	57.9	44.4
Survivors without MBD, n/N	1/1	19/25	196/251	460/558	737/907	1,413/1,742
Percent of total survivors	100	76.0	78.1	82.4	81.3	81.1

GA, gestational age; NICU, neonatal intensive care unit; MBD, major brain damage; N, number of patients with a known brain ultrasound before discharge.

vors was higher than the proportion of survivors without MBD relative to the total number of admitted patients and it was independent of GA.

A total of 1,440 patients (44.5%) died. Data regarding EoL decisions were available for 1,170 patients (81.3%). EoL decisions preceding death were documented in 432 patients (36.9%), and they were more frequently implemented among the most immature infants (i.e., 42.9, 51.1, 39.1, 33.2, and 28.8% for those at 22, 23, 24, 25, and 26 weeks' GA, respectively). The main causes of death differed between the EoL group and the group of patients for whom "full therapy" was maintained until death (Table 3). In spite of the fact that sometimes the main cause of death was attributed to a nonneurological condition, MBD was present in 256 patients (59.3%) for whom there was limitation of therapy and in 186 (25.2%) for whom full therapy was continued until death ($p < 0.001$). Finally, the length of hospital stay [median (IQR)] in survivors was 92 (77–112) days, compared to 5 (1–15) days in patients who died; no difference was found between infants who had limitation of therapy [6 (2–15) days] and those for whom it was maintained until death [6 (1–16) days].

Table 3. Distribution of causes of death among patients in whom therapy was withheld or withdrawn and among those in whom full therapy was maintained until death

Principal cause of death, %	Limitation of therapy (*n* = 432)	Full therapy (*n* = 738)	*p*
Respiratory	26.6	43.8	
Sepsis	16.2	27.8	
Neurological	34.0	4.9	<0.001
Others	19.9	16.9	
Missing	3.2	6.6	

Discussion

Although many biological and environmental factors may contribute to the future neurodevelopment of extremely preterm infants, the variable most frequently associated with a poor outcome is early brain injury [16, 17]. Our study shows that the probability of survival without MBD detected by CUS among patients admitted to the NICU is higher relative to the total number of survivors than to the total number of NICU-admitted patients and/or the total number of live-born infants. Additionally, we found that these probabilities are not significantly associated with GA. We also found that most deaths among extremely preterm infants take place in the first 2 weeks of life, such that most resources are invested in patients who ultimately survive.

A small proportion of the live-born patients in our study (4%) died in the delivery room (Table 1). The decision to limit intervention had been made for most of those who died (88%). Whether this decision was made antepartum in consensus with the parents, or immediately after birth because of the extreme immaturity and poor clinical condition of the neonate, was not systematically recorded. However, the lower rates of both antenatal steroid administration and C-sections in this group might indicate that the majority of the decisions were made before birth. After full resuscitation and NICU admission had been decided upon, subsequent major complications were handled by a thorough patient evaluation and discussion with the family whenever possible, and a decision to continue or modify the goals of care was reached. A frequent consideration under these circumstances is whether a different decision-making process would yield a different outcome. The EPICure and the EPIPAGE studies (population-based cohort studies that included long-term follow-up of preterm infants between 23 and 25 weeks' GA) found no significant differences in outcomes from different clinical approaches (including initial interventions after birth) [18]. Although mortality before NICU admission was lower in the EPICure study (25%) than in the EPIPAGE study (34%), the mortality rates after admission were reversed (45 vs. 29%, respectively), and no overall differences in survival at hospital discharge were observed after adjusting for GA. The risk of severe brain injuries in hospitalized patients was 24% in both studies, whereas among survivors it was 17% in the EPICure study and 11% in the EPIPAGE study. Furthermore, at 24–30 months of age the risk of cerebral palsy was 20 versus 16%, respectively, and at 5–6 years the rate of cognitive delay (score <70 on the Kaufman ABC test) was 10 versus 14%, respectively. The authors concluded that, despite the apparent differences in modalities of limitations of intensive care, the results did not vary significantly in the population of extremely preterm infants from 23 to 25 weeks' GA. In our study, considering the same category of patients (23–25 weeks), MBD must have played an important role in mortality, either directly or as a result of the redirection of therapeutic efforts, since its incidence among patients admitted to the NICU was 33.5% (562/1,676 infants with CUS before discharge), whereas among survivors it was 19.1% (159/834). These results are similar to the EPIBEL study, with respective MBD incidences of 31.8 and 20.6% [5].

Caring for patients at the threshold of viability and their families is complicated by great individual variability among pregnancies and neonates, and the many biological, psychological, social, economic, and legal factors involved. Prognosis research in this field is especially difficult to design and interpret due to its observational nature and to multiple potential comorbidities [19]. The concept of the "limit of viability" is controversial in itself [20], and decisions in the "grey zone" may fall under therapeutic obstinacy or, conversely, under failure to provide therapy that might result in a better outcome than predicted. Many parents feel more comfortable with the knowledge that they "gave their baby a chance". This may represent a sensible intermediate course of action and, from an ethical point of view, helps ensure clinical care for patients with potentially good prognoses despite their extreme prematurity; it also prevents taking away hope from families before complications have actually occurred [21].

Our study has the limitations inherent to a multicenter networking study, with approximately 60 facilities contributing data. The data reliability relies on the accuracy of patients' records, which might be limited. In addition, it was not possible to take into account differences in hospital resuscitation protocols or NICU care, which have been shown to result in variations in rates of survival and survival without impairment [22]. Our data merely depict clinical practice in most tertiary NICU in Spain. The diagnosis of MBD was based on CUS findings because this technique was widely available and systematically used in all of the participating centers. Serial CUS is the method of choice for sick preterm infants in the NICU and it is highly effective in diagnosing severe GM-IVH (grade 3) and IVH complicated by parenchymal infarction (grade 4), as well as severe white-matter lesions such as periventricular leukomalacia [23, 24]. Although MRI at discharge or term-equivalent age is able to detect subtle white-matter abnormalities better and more reliably depicted than CUS, a single MRI at this age will not identify minor hemorrhages or smaller cystic lesions that may have resolved between birth and discharge, a period that can be longer than 3 months in these infants. Furthermore, the feasibility of MRI is limited due to logistic issues and because it often requires infant sedation to avoid display movement artifacts, making interpretation difficult and being inferior to good-quality sequential CUS.

Another limitation of our study is that we did not consider the presence of other morbidities, such as retinopathy of prematurity or bronchopulmonary dysplasia, which may negatively impact future neurodevelopment. Finally, our study only examines survival and survival without MBD detected by CUS and lacks long-term follow-up of the surviving children to evaluate their neurological and neurodevelopmental status. A recent study showed an increase over time in the survival of infants born at 22–24 weeks' GA, without improvement in the neurological outcome [25]. Another, however, reported a survival rate of 100% for patients with a GA of 22 weeks admitted to the NICU, without cerebral palsy at 18 months' corrected age and with normal developmental quotients in 50% of them [26]. In addition, the EPICure study, with evaluations of survivors at 6 years of age, showed that although there appeared to be a reduction in the cognitive performance scores of infants from 23 to 25 weeks' GA, after adjusting for sex this trend was not significant [27]. Nevertheless, in contrast to the original EPICure study, the evaluation at 3 years of age of a more recent cohort of patients by the same group (EPICure 2) showed improvement in survival and survival without disability, but the proportion with disability increased significantly with decreasing GA at birth, from 45% at 22–23 weeks' GA to 30% at 24 weeks, 25% at 25 weeks, and 20% at 26 weeks [28].

In conclusion, in newborns at the limit of viability the proportion of survivors without MBD detected by CUS is higher when referred to the total number of survivors instead of the total number of births and it seems to be independent of GA. Our data suggest that EoL decisions and redirection of care after the occurrence of MBD might play an important role in this respect. Although the long-term prognosis cannot be based only on ultrasonographic lesions, these results could support the attitude of "giving an opportunity" even to the most immature patients, if this is in accordance with the parents' wishes.

Acknowledgements

The authors thank all of the investigators and coordinators of the SEN1500 Neonatal Network, and the presidents, vice-presidents, and members of the SEN1500 Commission.

Thanks also go to the hospitals and researchers from the SEN1500 Network of the Spanish Neonatal Society: Complejo Hospitalario Albacete (Andrés Martínez Gutiérrez), Hospital U. de Basurto (Alberto Pérez Legorburu), Hospital Bierzo (María Teresa Prada), Hospital Cabueñes (Rafael García Mozo), Hospital Carlos Haya (Tomás Sánchez Tamayo), Hospital General Castellón (Ramón Aguilera Olmos), Hospital Central Asturias (Belén Fernández Colomer), Hospital Clínic Barcelona (Josep Figuera Aloy), Hospital Clínico San Carlos (Araceli Corredera Sánchez), Hospital Cruces (Amaya Rodríguez Serna), Hospital U. Donostia (M. Ángel Cortajarena Altuna), Hospital Elche (Josep Mut Buigues), Hospital General de Cataluña (Laura Castells Vilella), Hospital G. de Granollers (Israel Anquela Sanz), Hospital Germans Trias i Pujol (W. Coroleu), Hospital Getafe (Lucía Cabanillas Vilaplana), Hospital Infanta Margarita (José María Barcía Ruiz), Hospital Jerez (Dolores Esquivel Mora), Hospital Juan Ramón Jiménez (José Ángel Morilla Sánchez), Hospital Juan XXIII (Mar Albújar), Hospital León (Emilio Álvaro Iglesias), Hospital Miguel Servet (Segundo Rite Gracia), Corporació Parc Taulí (Juan Badia), Hospital San Juan de Deu (Martín Iriondo Sanz), Hospital San Pedro de Logroño (Inés Esteban Díez), Hospital San Pedro de Alcántara (Ma Jesús López Cuesta), Hospital de la Santa Creu i Sant Pau (Gemma Ginovart Galiana), Hospital Severo Ochoa (María José Santos Muñoz), Hospital Txagorritxu (María Mercedes Martínez Ayucar), Hospital Universitario Arnau de Vilanova (Eduard Solé Mir), Hospital Valme (Antonio Gutiérrez Benjumea), Hospital Virgen de la Concha (Víctor Marugán Isabel), Hospital U. Virgen de la Macarena (Mercedes Granero Asencio), Hospital Virgen de la Salud (Alicia de Ureta Huertas), Hospital U. Virgen de las Nieves (Ma Fernanda Moreno Galdó), Hospital Xeral Vigo (María Suárez Albo), Hospital Universitario de Valencia (Javier Estañ Capell), Hospital Universitario de Zaragoza (Purificación Ventura Faci), Hospital Universitario Santiago (Ma Luz Couce Pico), Hospital General de Burgos (Cristina de Frutos Martínez), Hospital General Universitario Alicante (Miriam Salvador Iglesias), Hospital Universitario de Fuenlabrada (Laura Domingo Comeche), Hospital Universitario Gregorio Marañón (Amparo Rodríguez Herreras), Hospital Universitario La Paz (Ma Dolores Elorza), Hospital Materno Infantil de Canarias (Lourdes Urquía Martí), Hospital Universitario Canarias (Pedro A. Fuster Jorge), Hospital Universitario de San Cecilio (Eduardo Narbona), Hospital Universitari i Politecnic La Fe (Isabel Izquierdo Macián), Hospital Universitario Reina Sofía (Juana María Guzmán Cabañas), Hospital Universita-

rio Río Hortera (Ma Mar Montejo Vicente), Hospital Universitario Salamanca (Pilar García González), Hospital Universitario Virgen del Rocío (Carmen Macías Díaz), Hospital Universitario Dexeus (Roser Porta), Scias-Hospital Barcelona (Silvia Martínez-Nadal), Hospital Josep Trueta (Alberto Trujillo), Complejo Hospitalario Universitario de Pontevedra (Javier Vilas González), Hospital Universitario de Ciudad Real (Miguel Ángel Cabezas), Hospital Puerta del Mar (Antonio Segado Arenas), and Hospital Doce de Octubre (Carmen R. Pallás Alonso).

Disclosure Statement

None of the authors declares having conflicts of interests.

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