Impact of cardiopulmonary resuscitation on extremely low birth weight infants

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Objectives
To examine whether extremely low birth weight (ELBW) infants who undergo Cardiopulmonary Resuscitation (CPR) in the delivery room present poorer survival and greater short-term neurological and general morbidity than those who do not.

Methods
In a retrospective cohort of 150 ELBW infants born at our hospital between 2000 and 2004, those who needed CPR and those who did not were compared for mortality and short-term general and neurological morbidity. Infants with major birth defects, suspicion of genetic disease and those without a proactive perinatal attitude in the delivery room were excluded. CPR was defined as the administration of chest compressions and/or epinephrine in the delivery room.

Results
150 infants were included, with gestational ages of 23-27 weeks (mean 25.6 ± 1.2), birth weight of 425-995 grams (mean 745.2 ± 132). Delivery room CPR was given to 32 infants (21.4 %). No differences in perinatal characteristics were found except for lower pH and Apgar score and a higher SNAPPE score in infants who underwent CPR. Survival at discharge was similar (62.5 % vs 76.3 % for those without CPR). Infants who received CPR needed more surfactant, oxygen and higher median airway pressure than infants who did not. Air leaks and coagulopathy were more frequent in CPR infants (p < 0.01). Prevalence of bronchopulmonary dysplasia, necrotizing enterocolitis and retinopathy was similar in the two groups. No statistical differences between ELBW infants who needed CPR and those who did not were found in prevalence of intraventricular haemorrhage (IVH) (62.5 % vs 52.5 %), IVH III (31.2 % vs 17.7 %), periventricular haemorrhagic infarction (PHI) (18.7 % vs 11 %) or cystic periventricular leucomalacia (PVL) (15.6 % vs 11 %). However, in a combined analysis of neurological morbidity (IVH III and/or PVL and/or PHI), significant differences between the two groups were found (46.7 % vs 21.6 %; p = 0.01).

Conclusion
This study does not support poorer survival or significant non-neurological morbidity during the neonatal period in ELBW infants who receive CPR. Although the prevalence of individual neurological problems was similar in the two groups, CPR was associated with a clear increase in general neurological morbidity, with a three-times greater risk of brain damage.

Key words:
Prematurity, Cardiopulmonary resuscitation, Brain damage, Intraventricular haemorrhage, Periventricular leucomalacia, Periventricular haemorrhagic infarction.

IMPACTO DE LA REANIMACIÓN CARDIOPULMONAR AVANZADA EN RECIÉN NACIDOS PRETÉRMINO DE EXTREMADO BAJO PESO

Objetivos
Examinar si los recién nacidos de extremado bajo peso (RNEBP) que reciben reanimación cardiopulmonar avanzada (RCPA) en la sala de partos presentan peor supervi-
vención y mayor morbilidad neurológica y global a corto plazo que aquellos que no la recibieron.

Métodos
En una cohorte retrospectiva de 150 RNEBP, nacidos en nuestro hospital entre los años 2000 y 2004, se comparó mortalidad y morbilidad global y neurológica a corto plazo entre aquellos que precisaron RCPA y los que no. Se excluyeron los nacidos con malformaciones y aquellos con limitación del cuadrante terapéutico en la sala de partos.

Resultados
Incluimos 150 niños, edad gestacional 23-27 semanas (25,6 ± 1,23), peso 425-995 g (745,2 ± 152). Recibieron RCPA en la sala de partos 52 (21,4%). Las características perinatales fueron similares, excepto pH y puntuación de Apgar inferiores, y puntuaciones mayores en la escala de Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE) en los niños con RCPA. La supervivencia al alta fue similar (62,5% frente a 76,3% en aquellos sin RCPA). Los pacientes con RCPA necesitaron más sufléteró- te, oxígeno y presión media en la vía aérea. Neumotórax y coagulopatía fueron más frecuentes en los niños con RCPA (p < 0,01). La frecuencia de displasia broncopulmonar, enterocolitis necrosante y retinopatía fueron similares en ambos grupos. La prevalencia de hemorragia intraventricular (HV) grado III (31,2% frente a 17,7%), infarto periventricular hemorrágico (IPH) (18,7% frente a 11 %), leucomalacia periventricular (LPV) (15,6% frente a 11 %), no difirió entre los RNEBP que precisaron RCPA y los que no. Sin embargo, el análisis combinado de morbilidad neurológica (HV grado III y/o LPV y/o IPH) mostró diferencias significativas entre ambos grupos (46,7% frente a 21,6%; p = 0,01).

Conclusión
La RCPA en RNEBP no parece implicar un aumento de la mortalidad neonatal ni de la morbilidad significativa no neurológica. Aunque la prevalencia individual de problemas neurológicos fue similar entre ambos grupos, la RCPA conllevó un claro aumento de la morbilidad global neurológica, incrementando tres veces el riesgo de lesión del SNC.

Palabras clave:
Prematuridad, Reanimación cardiopulmonar, Lesión cerebral, Hemorragia intraventricular, Leucomalacia periventricular, Infarto periventricular hemorrágico.

INTRODUCTION
In recent years there has been a marked increase in the number of extremely low birth weight (ELBW) in- fants, weighing under 1,000 grams and with a gestational age under 28 weeks. The guidelines for cardiopulmonary resuscitation of neonates do not stipulate any specific rec- ommendations that take weight or gestational age into ac- count. Therefore, in the population of ELBW infants, the same indications for the start of profound or advanced cardiopulmonary resuscitation are used as in all other neonates, i.e. cardiac massage and/or adrenalin and other drugs. The frequency of advanced cardiopulmonary resuscitation in this ELBW group varies between 6 and 12.5%, according to the literature. The vulnerability of the ELBW infant means that CPR may involve greater mortality and high short-term mor- bidity. In general, in ELBW infants, cardiac massage and/or adrenalin administration are seen as risk factors for poor survival and severe intraventricular haemor- rhage. However, since data in the literature on mor- bidity in relation to advanced resuscitation in this population group are scarce, the risk/benefit relationship of CPR in this age group is not well established. The study of short- and long-term neurological morbidity as- sociated with CPR in ELBW infants is important not only to optimize indications, guidelines and limits of CPR in these neonates, but to establish whether the CPR at birth leads to a specific group of ELBW infants at high neu- rondevelopmental risk.

The aim of this study was to examine whether the ELBW infants, under 28 weeks gestational age and weigh- ing under 1,000 grams at birth, who need CPR in the de- livery room, have worse survival and greater neurological and general short-term morbidity during the neonatal pe- riod.

MATERIAL AND METHODS
Design
A retrospective cohorts study, conducted by exhaus- tive review of medical records.

Subjects
We included all neonates weighing under 1,000 grams at birth and under 28 weeks gestational age (estimated by amenorrhea) born at our hospital between September 2000 and September 2004. Neonates with major congeni- tal defects and those without a proactive perinatal attitude in the delivery room were excluded.

Setting
The study was conducted in a university hospital which attends the annual birth of 10,500 infants, 1.4% of them premature under 1,500 grams. In the period of time cov- ered by the study, the standard practice of CPR in ELBW infants remained unchanged at the hospital. The resusci- tation of this group of neonates was performed by a staff neonatologist, one or two doctors in training and a spe- cialized nurse in neonatal resuscitation.

Main objective
To examine whether ELBW infants, under 28 weeks gestational age and weighing under 1,000 grams at birth, who needed CPR in the delivery room, had worse sur- vival and greater short-term neurological and general morbidity during the neonatal period. Primary end-points

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were established as survival at discharge and initial neurological damage (severe intraventricular haemor-
 rhage, haemorrhagic periventricular infarction and cystic
 periventricular leucomalacia). In addition, a combined in-
dex of neurological morbidity, in which the three disor-
ers mentioned were included, was established. Other
secondary points examined were haemodynamic insta-
bility, the need for exogenous pulmonary surfactant, the
need for mechanical ventilation, the persistence of duc-
tus arteriosus with clinical repercussions, air leaks, coag-
ulopathy, early sepsis and necrotizing enterocolitis. Fur-
ther secondary points examined were the hospital stay,
time on oxygen therapy, bronchopulmonary dysplasia,
total duration of mechanical ventilation, inotropic sup-
port, prevalence retinopathy of prematurity needing
lasertherapy, age at which enteral nutrition began and
port, prevalence retinopathy of prematurity needing
survival at discharge and initial neurological damage
(cystic evolution that extends to the cortico-subcortical
region; and grade 4, cystic evolution that extends to the
fronto-parietal and/or occipital
periventricular regions; and grade 4, cystic evolution that
extends to the cortico-subcortical region). Haemorhagic
periventricular infarction (HPI) was diagnosed on ob-
servation of a hyperechogenic, globulous image, half
moon-shaped or triangular, generally unilateral, with an
extension from the outside angle of the lateral ventricle
up to the cortico-subcortical region12. The Score for
Neonatal Acute Physiology Perinatal Extension (SNAPPE)
was designed as a scale to reflect the gravity of the status
of the neonate during the first 24 hours of life and has
been proved as very useful in establishing the risk of
death, the development of chronic pulmonary disease
and the duration of hospital stay13-15. We assessed the
gravity of the patients in their first twelve hours of life by
means of their SNAPPE-II score.

The background of chorioamnionitis was considered
when the mother had at least two of the following crite-
ria: temperature > 38 °C, neutrophil leukocytosis and/or
high acute phase reactants, or when it was shown in the
pathological analysis of the placenta.

The diagnosis of intraventricular growth retardation was
established when the weight development of the child
at birth was below percentile 3 for his/her gestational age13.

Cardiac echography was used to test for ductus arte-
rioso in those infants with clinical suspicion. Haemody-
namic instability was classified by the number of inotrop-
ic drugs necessary and/or the need for corticotherapy. We
consider the presence of coagulopathy on transfusion of
frozen fresh plasma and/or platelets being needed in the
first twelve hours of life. Necrotizing enterocolitis was
measured according to the modified Bell scale16. We de-
fined bronchopulmonary dysplasia as the need for sup-
plementary oxygen therapy at 36 weeks of corrected ges-
tational age. A day with supplementary oxygen was
defined as one on which oxygen was needed at a con-
centration over 21 % for over twelve hours17. Retinopa-
thy was measured according to the international scale18.

Statistical analysis
The categoric or qualitative data were expressed as ab-
solute frequencies and as percentages; and quantitative
data, through the mean, the median and standard devia-
tion. Categorical variables were compared through the
Chi-squared test or the Fisher exact test. To compare two
groups of quantitative data, the Student’s t and the U
Mann-Whitney tests were used, depending on whether
the data were normally distributed or not. A value was
considered significant when p was < 0.05. Data were
analysed with the SPSS 10.0 (SPSS Inc.) statistical pro-
grame.

The study was approved by the Clinical Research Ethics
Committee of La Paz University Children’s Hospital, Madriñ.

RESULTS
The population included in the study consisted of
150 infants with gestational ages between 23 and
27 weeks (mean 25.6 ± 1.2), with birth weight between
425 and 995 grams (mean 745.2 ± 132). CPR was given to
32 infants (21.4%). The perinatal characteristics of the two
groups were comparable (table 1). Apgar score at one
minute and 5 minutes and cord pH were significantly
lower in the group that received CPR. Only 9.37 % had a
zero Apgar score in the first minute of life. 59.4 % of the
infants with CPR had an Apgar < 3 and 90.6 % had an Ap-
gar < 5 in the first minute of life versus 11.8 % and 50.8 %
of the infants who did not need CPR. Similarly, the infants in the CPR group had higher scores on the SNAPPE-II scale of gravity in the first twelve hours of life (table 2).

We found no differences in the obstetric backgrounds recorded and the incidence of chorioamnionitis was similar in both groups (table 1). During the first week of life we found no differences in the type and duration of respiratory support, haemodynamic instability, persistent ductus arteriosus with clinical repercussions or early sepsis. However, air leaks and coagulopathy were more common in the group of children with CPR. The children who received CPR needed higher doses of exogenous pulmonary surfactant, higher oxygen inspired fraction and higher median airway pressure during the first 72 hours of life (table 2). The presence of stage II-III necrotizing enterocolitis was similar in both groups (table 2).

Moving on to late neonatal morbidity, we found no significant differences in the frequency of bronchopulmonary dysplasia (37.5% vs 39%), retinopathy of prematurity needing laser photocoagulation (12.5% vs 13.5%) and days of hospital stay (75.90 ± 134.1 vs 81.17 ± 45.95). Weight and head perimeter on discharge were similar in the two groups. No differences were found at the moment of starting enteral nutrition or in the age at which exclusive enteral nutrition was reached. Survival on discharge showed no significant differences, being 62.5% in the children who received CPR vs 76.5% in those who did not. Nor did we find statistical differences on comparing the two groups for mortality in the first three days of life (18.75% vs 8.47%).

The presence of clinical convulsions was the same in both groups. Cerebral ultrasonography was performed on 96.6% of the infants. We found no statistically significant differences for the presence of any degree of IVH. IVH grade III, haemorrhagic periventricular infarct (HPI) or PVL (Periventricular Leucomalacia), CPR (Cardiopulmonary Resuscitation).

### Table 1. Perinatal characteristics of the two groups, expressed as mean and standard deviation for quantitative variables and as a percentage for qualitative variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>ELBW Infants with CPR</th>
<th>ELBW Infants without CPR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (weeks)</td>
<td>25.06 ± 1.26</td>
<td>25.57 ± 1.35</td>
<td>0.575</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>704.1 ± 134.1</td>
<td>754.6 ± 125.6</td>
<td>0.598</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>54.2%</td>
<td>40.6%</td>
<td>0.231</td>
</tr>
<tr>
<td>IUGR</td>
<td>26.5%</td>
<td>6.3%</td>
<td>0.289</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>22.2%</td>
<td>51.5%</td>
<td>0.245</td>
</tr>
<tr>
<td>In utero steroidinosis</td>
<td>20.5%</td>
<td>21.9%</td>
<td>0.800</td>
</tr>
<tr>
<td>Prenatal corticoids</td>
<td>57.6%</td>
<td>55.6%</td>
<td>0.901</td>
</tr>
<tr>
<td>Caesarean</td>
<td>46.6%</td>
<td>56.3%</td>
<td>0.901</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>21.2%</td>
<td>18.8%</td>
<td>0.766</td>
</tr>
<tr>
<td>Amniorrhesis (hours)</td>
<td>67.05 ± 134.9</td>
<td>36.51 ± 109.9</td>
<td>0.498</td>
</tr>
</tbody>
</table>

GA (gestational age), IUGR (intrauterine growth retardation).

### Table 2. Apgar score, cord pH and SNAPPE-II score

<table>
<thead>
<tr>
<th>Variable</th>
<th>ELBW Infants with CPR</th>
<th>ELBW Infants without CPR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apgar 1 minute</td>
<td>7.24 ± 0.10</td>
<td>7.28 ± 0.11</td>
<td>0.017</td>
</tr>
<tr>
<td>Apgar 5 minutes</td>
<td>6.6 ± 1.7</td>
<td>6.77 ± 1.40</td>
<td>0.001</td>
</tr>
<tr>
<td>SNPPE II scale</td>
<td>72.25 ± 22.92</td>
<td>52.90 ± 24.58</td>
<td>0.001</td>
</tr>
<tr>
<td>Surfactant (dose)</td>
<td>1.77 ± 0.49</td>
<td>1.50 ± 0.76</td>
<td>0.005</td>
</tr>
<tr>
<td>MAP (cm H2O)</td>
<td>5.20 ± 0.24</td>
<td>4.59 ± 0.17</td>
<td>0.001</td>
</tr>
<tr>
<td>maximum P02</td>
<td>0.90 ± 0.22</td>
<td>0.70 ± 0.24</td>
<td>0.005</td>
</tr>
<tr>
<td>± 2 vasoactive drugs</td>
<td>54.6%</td>
<td>28.0%</td>
<td>0.076</td>
</tr>
<tr>
<td>Air leaks</td>
<td>25%</td>
<td>5.9%</td>
<td>0.004</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>56.5%</td>
<td>20.4%</td>
<td>0.001</td>
</tr>
<tr>
<td>Encephaloxia</td>
<td>6.4%</td>
<td>10.9%</td>
<td>0.113</td>
</tr>
<tr>
<td>Early sepsis</td>
<td>12.5%</td>
<td>6.8%</td>
<td>0.205</td>
</tr>
</tbody>
</table>

MAP (Median airway pressure). P02 (Inspired oxygen fraction).

### Figure 1. Short-term neurological morbidity in both groups, expressed as percentages. IVH (Intraventricular haemorrhage), HPI (Haemorrhagic Periventricular Infarction), PVL (Periventricular Leucomalacia), CPR (Cardiopulmonary Resuscitation).
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In originating brain damage in pre-term neonates the kind of delivery, but also for the frequency of characteristics such as the frequency of multiple delivery and only for weight, gestational age and other perinatal characteristics during the neonatal period. Additional evidence that CPR in ELBW infants is associated with greater overall neurological morbidity during the first 72 hours. In addition, they had greater frequency of air leaks and coagulopathy. However, despite this higher early morbidity of the group needing CPR, there were no differences between the two groups in overall morbidity, whether respiratory, haemodynamic, gastro-intestinal, ocular, or in length of hospital stay. The increased early respiratory morbidity associated with CPR was also seen in an earlier study including 158 neonates <1500 g.

In our study, survival was similar in the two groups (62.5% vs 70.5%), result that is consistent with other studies on the question. Although the data available indicate that most ELBW infants with CPR survive, the analysis of this question in large populations reveals that CPR is associated with a greater probability of death in the neonatal period comparing with infants who do not need CPR in all weight categories except the 401-500 gram subgroup. The main concern after CPR in this especially vulnerable group of premature infants is that the CPR intervention might be accompanied by neurological lesion and subsequent long-term neurological morbidity. Although this is encouraging, it must be noticed that brain ultrasonographic disorders cannot be directly compared with neurodevelopmental disorders, since other factors or conditions not detected by brain ultrasonography contribute to the infant's final neurodevelopment. The frequency of PVL in this study is hard to compare with other similar studies due to the differing criteria used by other authors to establish this diagnosis and perhaps because of scant uniformity in the time chosen for ultrasonographic examination. In our study, the diagnosis of PVL was established on the basis of the evolution of ultrasonographic findings throughout the admission in Neonatology and especially the last available echography.

The low number of ELBW infants with CPR in our study limited statistical power and prevented stratification of the results by weight groups (<750 g vs 750 to 1000 grams). In addition, the retrospective design of the study suggests that the indications, duration and aggressiveness of CPR may have been heterogeneous. The association between CPR and brain damage is not necessarily causal and sequential, since the need for CPR and way pressure and higher oxygen inspired fraction during the first 72 hours. In addition, they had greater frequency of air leaks and coagulopathy. However, despite this higher early morbidity of the group needing CPR, there were no differences between the two groups in overall morbidity, whether respiratory, haemodynamic, gastro-intestinal, ocular, or in length of hospital stay. The increased early respiratory morbidity associated with CPR was also seen in an earlier study including 158 neonates <1500 g.22

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**Figure 2. Combined neurological index (IVH grade III and/or HPI and/or PVL ≥ grade 2) in both groups, expressed as percentage.**

Differences between the two groups (46.7% vs 21.6%; p < 0.001), with OR 3.18 (1.37-7.39, 95% CI) (fig. 2).

**Discussion**

Due to the vulnerability of ELBW infants, studies that examine the effects and consequences of cardiovascular resuscitation on the central nervous system are needed.4,5 This retrospective study of a broad population contributes additional evidence that CPR in ELBW infants is associated with greater overall neurological morbidity during the neonatal period.

The characteristics of the two groups were similar, not only for weight, gestational age and other perinatal characteristics such as the frequency of multiple delivery and the kind of delivery, but also for the frequency of choroamnionitis, a factor that may play an important role in originating brain damage in pre-term neonates.4,5

In our population, the frequency of CPR in ELBW infants was 21.4%, a prevalence somewhat higher than that reported in other studies.4,5 As was to be expected, the Apgar scores at one and at five minutes were markedly lower in the group of infants who needed CPR. Only 9.37% of these had an Apgar score of zero in the first minute of life and 59.6% had a score <3. The remaining infants in this group had Apgar scores from 3 to 5 inclusive, and it is likely that some of these neonates did not meet the international recommendations for the start of cardiac massage and/or administration of epinephrine during resuscitation. The ELBW infants who needed CPR had greater early neonatal morbidity, with worse physiological stability and greater clinical gravity in the first 12 hours of life expressed by higher scores on the SNAPPE, and more surfactant doses, greater median air

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expected that it happens, probably, with greater frequency than expected, apart from that intact survival is possible and long-term evolution of premature babies weighing <1,500 grams who needed CPR is not shown. Rather, our study provides further evidence that over half the ELBW infants who undergo CPR suffer no significant brain damage, IVH grade III, IPIH or PVL. These data are relevant when weighing benefits and risks of CPR in this group, information that is important when we define our interventions and also at the pre-delivery interview with the parents. However, CPR in ELBW infants must also be noticed as there are very few studies on the long-term evolution of premature babies weighing <1,500 grams who needed CPR and the populations studied are small. This does not allow us to reach clear conclusions, apart from that intact survival is possible and that it happens, probably, with greater frequency than expected.[1-3]

CONCLUSION

In summary, in our scope CPR in ELBW infants clearly signifies increased risk of brain damage, but not of greater non-neurological morbidity during the hospital stay. However, in this study as in others published in recent years, the high mortality and the high percentage of severe lesions or sequelae traditionally associated with CPR in ELBW infants are not shown. Rather, our study provides further evidence that over half the ELBW infants who undergo CPR suffer no significant brain damage, IVH grade III, IPIH or PVL. These data are relevant when weighing benefits and risks of CPR in this group, information that is important when we define our interventions and also at the pre-delivery interview with the parents. However, CPR in ELBW infants must also be noticed as a potential factor of biological risk of adverse neurodevelopment when both short and long-term evolution of these newborns are examined.

REFERENCES


