Prognostic factors and survival in neonates with congenital diaphragmatic hernia

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Abstract

Objective: to evaluate the prognostic factors importance to survival in neonatal period of newborns with congenital diaphragmatic hernia treated at Hospital das Clínicas, School of Medicine of Universidade de São Paulo, and to compare the outcome with data published in medical literature. So that the results of this study might allow updating family counseling and guiding changes in clinical management of our department.

Methods: retrospective study of 27 consecutive newborns with congenital diaphragmatic hernia admitted to the Pediatric Surgery Department of Instituto da Criança, School of Medicine of Universidade de São Paulo, from April 1991 to January 2002, and statistical comparison with medical literature metaanalysis data.

Results: of 27 patients, 15 were born at our institution and 12 were admitted by transference after birth. Twelve (44%) have had congenital diaphragmatic hernia diagnosed prenatally and 23 (85%) were full-term newborns. Most patients presented early respiratory distress and needed intubation at delivery room. Six newborns presented criteria for indication of extracorporeal membrane oxygenation. Twenty patients (74%) were submitted to operative repair and seven (26%) died without the minimal clinical stabilization necessary for surgical procedure (five of these patients reached criteria for indication of extracorporeal membrane oxygenation). The postoperative mortality was 25% (5/20). The overall survival of neonatal period was 56% (15/27). The survival of patients that were born at our hospital was 33% (4/12), and the survival of the newborns admitted by transference was 73% (11/15). Severe respiratory distress, early indication to mechanical ventilation and severe hypoxemia (post-ductal pO2 < 100 mmHg despite all efforts) were identified as predictors of bad outcome with statistical significance.

Conclusion: our high mortality rate of newborns with congenital diaphragmatic hernia is statistically similar to that described in international publications. In the group of non-responsive patients to standard treatment available, the use of extracorporeal membrane oxygenation should be able to reduce mortality. The impact of this therapeutical strategy in the overall survival depends on other factors that were not analyzed in the present study. Family counseling of patients' parents on congenital diaphragmatic hernia in our department may follow the same patterns referred in world medical literature.


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Introduction

The treatment of newborns with congenital diaphragmatic hernia (CDH) is still a challenge for pediatric surgeons and neonatologists.

In the last decades, advances in the therapy of primary pulmonary hypertension (PPH) in newborns, such as mild
ventilation with permissive hypercapnia,1,2 high-frequency oscillatory ventilation (HFOV),3 use of nitric oxide (NO) as selective pulmonary vasodilator4 and extracorporeal membrane oxygenation (ECMO).5-6 were incorporated into the treatment of newborns with CDH.

Similarly, the possibility of diagnosis by means of prenatal ultrasonography and the attempts of in utero intervention have opened up new possibilities of success.7-9 In spite of the initial reports indicating a reduction in mortality, some retrospective analyses did not confirm a significant impact on overall survival rate.10-12

The hypoplasia/pulmonary hypertension binomial remains as the principal mortality factor.13 Several prenatal and postnatal prognostic factors were described in order to define the severity of the disease and the individual chances of survival with the purpose of guiding medical conducts and family counseling approaches.14-20 Even though none of these parameters can be separately considered, a few of them are still accepted all over the world and are used for the comparative assessment of healthcare quality offered to these newborns.21

Recently, Beresford and Shaw presented a meta-analysis based on 35 publications related to the evolution of newborns or fetuses with diagnosis of CDH.22 In this assessment, they compared mortality data, relating them to the diagnosis and treatment developed. The summary of the results is shown in Table 1.

The purpose of our study was to analyze the importance of prognostic factors to the survival of patients with CDH in the neonatal period treated at the Hospital das Clínicas da Faculdade de Medicina da USP (HCFMUSP), and compare the results with the ones found in literature, allowing the collection of updated data that allow guiding family members and changing the conduct at our service.

Method


The treatment used in each case, according to the severity, included:

1) parenteral hydroelectrolytic and nutritional support;
2) hemodynamic and blood gas control through the catheterization of the umbilical, tibial or radial artery;
3) respiratory support through supplementary oxygen therapy, conventional mechanical ventilation with permissive hypercapnia, or high-frequency oscillatory ventilation;
4) use of exogenous surfactant, sedation, vasoactive drugs and inhaled nitric oxide;
5) surgical indication after clinical stabilization (delayed surgery).23-26

The prognostic factors analyzed were the following: respiratory distress at birth (Apgar score ≤ 6 in the fifth minute of life), need of early intubation (< 6 hours of life), persistent severe hypoxemia (postductal pO2 lower than 100 mmHg in spite of maximum therapy), association of severe somatic malformations, severe pulmonary hypertension (echocardiogram with gradient > 40 mmHg or repercussion on RV) and potential indication of ECMO (defined as pO2 < 50 mmHg for over four hours and absence of response to the conventional therapy available for newborns with weight over 2,000g without CNS hemorrhage and cardiac malformations or other malformations incompatible with life).27

The data referring to mortality and prognostic factors were analyzed and compared with the ones presented by Berersford et al., using the Yates-corrected chi square test or one-tailed or two-tailed Fisher’s exact test, in which a p values of 0.05 were significant.

This study was approved by the local Ethics and Research Committee.

Results

Twelve out of the 27 patients were born at our hospital, and 15 were transferred with an average interval of 3.2 days of life (15 hours - nine days). Twelve (44%) had a prenatal diagnosis, and 11 of them were born at the HCFMUSP. The average birthweight was 2,805 g (1,107 - 4,420 g), and 85% (23/27) of the babies were full term.

Complex congenital malformations were diagnosed in eight cases (30%), three (11%) of which involved cardiac malformations.

In relation to prognostic factors, 56% (15/27) presented Apgar score ≤ 6 in the fifth minute of life, and 59% (16/27) were early intubated (most of them in the delivery room). Pulmonary hypertension (PH) was assessed in the postoperative period through echocardiogram in 70% (19/27) of the patients. Among these, 50% presented severe PH.

Six children presented indication for ECMO, and seven (26%) died without reaching minimum clinical conditions for surgery. Among the patients who died in the preoperative phase, five would have been ECMO candidates, and the method would have been contraindicated in two due to low weight and severe cardiopathy. Postoperative mortality was 25% (5/20). No intraoperative deaths occurred.

The overall mortality rate in the neonatal period was 44% (12/27). The mortality rate of outpatient newborns was 27% (4/15) and among the ones who were born at the HCFMUSP, it was 67% (8/12).

The mortality rate in different subgroups - compared to the one described by Berersford and Shaw - is presented in Table 2. The analysis of prognostic factors in our patient population is shown in Table 3.
Discussion

The group of newborns with CDH treated at our institution in the study period is quite heterogeneous, including a wide range of patients, from children with mild respiratory distress and without other anomalies to patients with severe pulmonary hypoplasia and associated complex malformations. These differences partially explain the discrepancy between the mortality in the cases followed up from the prenatal period and born at our institution and the cases diagnosed and transferred after birth. The first group concentrates most newborns in serious conditions and with the worst prognosis. The lower mortality rate that occurred in the cases transferred after birth and without prenatal diagnosis may be attributed to selection bias, because many of the severe cases initially assisted at neonatology services with fewer therapeutic resources die before they can be transferred to specialized services and they are not, therefore, included in the statistics.28

Boloker et al. analyzed 120 consecutive cases of CDH treated at one single center with standardized therapy, and also found differences between the group of infants born at the institution and the babies transferred after birth, observing a lower incidence of severe malformations and lower mortality in the second group.29 They concluded that these differences would be related to preselection and that, excluding the cases with somatic and/or pulmonary malformations incompatible with life and the cases with neurological complications, it is possible to reach a survival rate greater than 80% through mild ventilation and delayed surgery, avoiding the mortality related to iatrogenic disorders.

Table 1 - Mortality calculated according to the stage reached by patients with CDH diagnosis, meta-analysis by Beresford et al.

<table>
<thead>
<tr>
<th>Data/ statistical study</th>
<th>Prenatal diagnosis</th>
<th>Live-born infants</th>
<th>NB submitted to surgery</th>
<th>Fetal death</th>
<th>Preoperative death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median mortality (IQR) *</td>
<td>58% (43-65)</td>
<td>48% (35-55)</td>
<td>33% (18-54)</td>
<td>10% (7-25)</td>
<td>27% (14-43)</td>
</tr>
<tr>
<td>Mean mortality (95% CI) †</td>
<td>56% (46-66)</td>
<td>47% (40-54)</td>
<td>36% (27-45)</td>
<td>14% (4-24)</td>
<td>30% (20-40)</td>
</tr>
<tr>
<td>n. of studies analyzed</td>
<td>9</td>
<td>20</td>
<td>27</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>n. of patients</td>
<td>285</td>
<td>844</td>
<td>794</td>
<td>212</td>
<td>538</td>
</tr>
<tr>
<td>n. of deaths</td>
<td>164</td>
<td>372</td>
<td>269</td>
<td>29</td>
<td>139</td>
</tr>
</tbody>
</table>

* interquartile range † 95% confidence interval

Table 2 - Comparison of the mortality in each subgroup between patients from ICr-HCFMUSP and meta-analysis by Beresford et al.

<table>
<thead>
<tr>
<th>Mortality</th>
<th>ICr-HCFMUSP</th>
<th>Beresford et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Live-born children</td>
<td>44% (12/27)</td>
<td>48% p = 0.87</td>
</tr>
<tr>
<td>2. Prenatal diagnosis</td>
<td>67% (8/12)</td>
<td>58% p = 0.74</td>
</tr>
<tr>
<td>3. NB with ECMO</td>
<td>83% (5/6)</td>
<td>44% p = 0.06 one tail</td>
</tr>
<tr>
<td>4. Children being prepared for surgery</td>
<td>26% (7/27)</td>
<td>27% p = 0.82</td>
</tr>
<tr>
<td>5. Children submitted to surgery</td>
<td>25% (5/20)</td>
<td>33% p = 0.55</td>
</tr>
</tbody>
</table>
By comparing the mortality in our patient population and the one in the meta-analysis published by Berersford and Shaw, we did not find any statistically significant difference in any of the subgroups analyzed. The mortality in our institution is, indeed, in most of the subgroups, numerically similar to the average described in literature.

Nevertheless, among the children with indication for ECMO, our mortality rate was almost twice as high as the one referred to in literature (83% versus 44%, one-tailed test p = 0.06). Depending on the sample size, it was not possible to establish statistical significance in this patient population. However, the confidence interval (95%CI) established for the mean mortality rate of the patients with indication for ECMO in the meta-analysis made by Berersford (34-50%) is quite distant from our mortality rate in this subgroup. Out of the seven children who died before reaching minimum clinical conditions for surgery, five presented indication for ECMO. These data suggest that the effective use of ECMO at our service could reduce mortality in the subgroups. The repercussion on the overall mortality rate depends, however, on the number of children admitted with indication for ECMO and of our effective results with the method.

The definition of reliable prognostic factors is a constant concern of the centers that treat patients with CDH. Based on these factors, it is possible to distinguish the children who effectively benefited from aggressive and costly therapies from the children to whom this treatment would only serve to prolong their suffering and their family’s as well.

Several prognostic factors were described by several centers, such as perinatal anoxia and early onset of symptoms, ventilation scores, lung compliance measurements, occurrence of pneumothorax as a consequence of aggressive ventilation, capability of reaching $pO_2 > 100$ mmHg, level of pulmonary hypertension, early antenatal diagnosis, size of the diaphragmatic defect, herniation of the liver into the thorax, association of cardiopathy and other complex malformations. These parameters relate to the severity of pulmonary hypoplasia and pulmonary hypertension. Therefore, the newborns with early and intense symptoms who were non-responsive to the therapy would present severe pulmonary malformations and other malformations of acutely difficult reversion, while in others pulmonary hypertension could be handled with different strategies, breaking the vicious cycle of aggravated PH - hypercapnia and hypoxemia - acidosis - PH.

Separately, no factor turned out to be ideal to predict survival in all institutions. This is a consequence of both the variability of the treatment employed at each center and the extreme clinical instability of these newborns, who may present sudden clinical deterioration due to the worsening of pulmonary hypertension.

Among the unfavorable prognostic factors classically referred to, statistical correlation was obtained, in our patient population, for the need of early intubation, Apgar score $\leq 6$ in the fifth minute of life, and impossibility of reaching $pO_2$ higher than 100mmHg in spite of maximum therapy. The other factors that were analyzed, even though they were numerically relevant, were not statistically significant due to the size of the analyzed sample.

We concluded that the mortality of newborns diagnosed with CDH remains high in our service, but at levels that are similar to the average published in international literature.

### Table 3 - Correlation between analyzed prognostic factors and mortality

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Mortality with factor</th>
<th>Mortality without factor</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intubation &lt; 6 hours of life</td>
<td>69%</td>
<td>9%</td>
<td>0.005*</td>
</tr>
<tr>
<td>2. Impossibility of $pO_2 &gt; 100$</td>
<td>100%</td>
<td>32%</td>
<td>0.01*</td>
</tr>
<tr>
<td>3. 5th minute Apgar $\geq 6$</td>
<td>67%</td>
<td>17%</td>
<td>0.02*</td>
</tr>
<tr>
<td>4. Severe PH on echocardiogram</td>
<td>67%</td>
<td>35%</td>
<td>0.12</td>
</tr>
<tr>
<td>5. Prenatal diagnosis</td>
<td>67%</td>
<td>27%</td>
<td>0.09</td>
</tr>
<tr>
<td>6. Associated severe malformation</td>
<td>62%</td>
<td>39%</td>
<td>0.40</td>
</tr>
</tbody>
</table>

* Statistically significant values.
In the group of patients that did not respond to standard treatment, the introduction of ECMO could reduce mortality. The repercussion of this measure on overall survival depends on other factors that were not analyzed in this study. The guidance of family members of patients with CDH in our service could follow the same standard referred to in the international literature.

References