Journal of Pediatric Surgery 50 (2015) 394–398

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Neurodevelopmental outcome in congenital diaphragmatic hernia survivors: role of ventilatory time

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ARTICLE INFO

Article history:
Received 8 March 2014
Received in revised form 8 May 2014
Accepted 25 May 2014

Key words:
Ventilatory strategy
Neurodevelopmental outcome
Congenital diaphragmatic hernia

ABSTRACT

Background: Neurodevelopmental impairment is one of the most significant morbidities among CDH survivors.
Purpose: Assess correlation between ventilatory time (VT) and short-term neurodevelopmental outcome in congenital diaphragmatic hernia (CDH) survivors.
Methods: A prospective longitudinal study was conducted between 2008 and 2012. Assessment of mental and motor development was performed at 6 and 12 months by Bayley Scales of Infant and Toddler Development — 3rd Edition (BSID-III). ROC curve analysis was used.
Results: Forty-two subjects were included in the study. There was a significant inverse correlation between neurodevelopment at 6 and 12 months and VT during first admission ($p < 0.0001$). VT predicting the risk of moderate (BSID-III <85) and severe (BSID-III <70) delay was 13 and 28 days, respectively (area under the curve — delay <85: 6 months mental 0.943 and motor 0.992; 12 months mental 0.877 and motor 0.925; delay <70: 6 months mental 0.934 and motor 0.943; 12 months mental 0.906 and motor 0.975; $p < 0.0001$).
Conclusions: VT should be considered an important marker to identify subjects at risk for short-term neurodevelopmental delay in CDH survivors. Early follow-up intervention therapy should be activated in every baby with a history exceeding 13 days of VT.

As long as survival of patients with congenital diaphragmatic hernia (CDH) has improved over the last 20 years, short and long term disabilities have become a key outcome measure for this patient population [1–3]. In particular, neurodevelopmental impairment is one of the most significant morbidities among CDH survivors and it is the focus of great clinical interest.

Although mechanical ventilation is usually required in such patients, few studies have addressed the relationship between neurodevelopmental outcome (NDO) in CDH survivors and mechanical ventilation [4]. In this respect, previous reports suggest that mechanical ventilation may be a surrogate marker for the degree of the underlying pulmonary hypoplasia which is considered the key determinant of outcome of children with CDH [5]. Hypothesizing that the longer ventilatory time the worse the outcome, we aimed to assess whether or not ventilatory time (VT) can be considered as a potential marker to identify CDH patients at risk for neurodevelopmental delay and whether or not a cut off value of ventilatory time exists.

1. Methods

All patients treated for major congenital anomalies at our Institution are offered a dedicated follow-up into a multidisciplinary outpatient clinic. All patients are prospectively evaluated at 6 and 12 months of age (corrected for gestational age). At each time point, a multidisciplinary team (neonatologist, neonatal surgeon, dedicated psychologist, pediatric neurologist, nurse) performs a full clinical and neurodevelopmental evaluation. For the purpose of our study we considered all patients treated for high-risk CDH (prenatal diagnosis and/or respiratory symptoms within 6 h of life) since March 2008 and with 6 and 12 month evaluations completed by December 2012.

Preterm infants (G.A. < 33 weeks) and those with a genetic syndrome or chromosomal anomaly known to be associated with neurodevelopmental delay were excluded.

Management of CDH patients in the postnatal period was conducted according to a standardized protocol which includes gentle ventilation, aimed at maintaining preductal oxygen saturations above 85%. Until March 2009, high frequency oscillatory ventilation was reserved to those neonates that continue to have hypercapnea

Abbreviations: AUC, area under the curve; BSID-III, Bayley Scales of Infant and Toddler Development — 3rd Edition; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; NDO, neurodevelopmental outcome; RCT, randomized control trial; ROC curve, receiver operating characteristic curve; VT, ventilatory time.

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http://dx.doi.org/10.1016/j.jpedsurg.2014.05.039
0022-3468/

refractory to conventional ventilation. Since March 2009, the infants were enrolled in a multicenter trial, randomized to conventional ventilation or high frequency oscillatory ventilation, and treated according to the guidelines of the CDH EURO Consortium study group [6]. In the study period, ECMO was not performed in our Institution. Surgical repair was delayed until clinical stability was obtained. Clinical data of children and socio-demographic data of the parents were collected during hospitalization. For each patient the following variables were recorded: gestational age, birth weight, prenatal diagnosis, liver in the chest at prenatal ultrasound and/or at surgery, associated anomalies, occurrence of sepsis (one or more septic episodes defined as positive blood cultures), VT, number of anesthesia, need for patch repair, and maternal and paternal education. In order to describe NDO in relation to VT, this was arbitrarily stratified into weeks (≤7 days, 8–14 days, 15–21 days, 22–28 days and >28 days).

Mental and motor development was assessed at 6 and 12 months using the Bayley Scales of Infant and Toddler Development — 3rd Edition (BSID-III) [7]. The BSID-III is an internationally recognized clinician administered tool designed to assess the development in very young children (1–42 months). It consists of three scales of which we used the cognitive and motor ones. The Cognitive Scale is made up of largely non verbal activities involving memory, problem solving, and manipulation. The Motor Scale is composed of the fine motor subtest, which measures visual–motor integration, visual spatial, and motor control skills of the hands, and the gross motor subtest, which measures large body complex movements and mobility.

This standardized test of infant development is age normed to have a mean of 100 and standard deviation of 15. Infants with a standard score between 84 and 70 were considered moderately delayed; those with a standard score <70 were considered very delayed.

Data were analyzed using GraphPad Prism 5.0 Macintosh Version (GraphPad Software, San Diego California USA, www.graphpad.com) and MedCalc® 12.7 Windows 7 Version (MedCalc Software bvba MedCalc Software, Ostend, Belgium). Student's t-test, χ^2 test, Pearson test and Spearman test were used as appropriate to assess associations and correlations between clinical and sociodemographic variables and NDO. Receiver operating characteristic (ROC) curve analysis was performed to determine the accuracy and the best cut-off value of VT to predict the risk of neurodevelopmental delay. ROC curve analysis was performed for both moderate to severe delay and only severe delay as the predicted outcome. The highest sensitivity was favored in choosing the optimal cut-off.

Results are reported as mean (standard deviation), median (interquartile range) or prevalence. Because four outcome measures (mental and motor NDO at 6 and 12 months) were tested against several hypothesized predictors, a Sydak-adjusted significance level of 0.001 was calculated to account for the increased possibility of type-I error. Two sided p values are reported.

The study was IRB approved and written parents' informed consent was obtained.

2. Results

During the study period, 67 children were treated for high risk CDH; out of 47 survivors, one had a gestational age of 32 weeks and was excluded from the study and four did not attend both follow-up appointments (6 and 12 months). The remaining 42 (87.5%) patients form the subject of this study. No data on NDO were available for patients not attending scheduled follow-up appointments. No statistically significant differences on base-line characteristics were observed between respondents and not-respondents. Mean age at follow-up appointments was 6 months and 11 days (range from 5 months and 20 days to 6 months and 25 days) and 11 months and 25 days (range from 11 months 10 days to 12 months and 7 days). Clinical and socio-demographic data of children are reported in Table 1.

The mean Mental Scale's scores were 92.0 (±15.1) and 96.5 (±13.7) at 6 and 12 months, respectively ($p = 0.0007$). The mean Motor Scale's scores were 92.2 (±16.9) and 92.9 (±17.2) at 6 and 12 months, respectively ($p = 0.6795$).

None of the considered variables reached statistically significant correlation with NDO with the exception of VT. An inverse correlation was found between VT during first admission and mental and motor development at 6 and 12 months (mental 6 months: $r = -0.6597$, $p < 0.0001$; motor 6 months: $r = -0.6821$, $p < 0.0001$; mental 12 months: $r = -0.5721$, $p < 0.0001$; motor 12 months: $r = -0.6860$, $p < 0.0001$). Table 2 compares NDO by VT.

VT was able to predict the risk of delay <85 and delay <70 as shown in Figs. 1 and 2, respectively.

3. Discussion

In our series of high risk non-ECMO-treated CDH survivors, we found that NDO was inversely correlated with VT during the first hospitalization. When considering NDO in high-risk CDH patients during the first year of life, incidence of impairment reported in literature varies considerably ranging from 12% to 77% and improving with age [4,8–12]. In particular some studies have addressed the influence of ECMO on NDO in CDH survivors. However as previously mentioned in our population such

Table 1
Clinical and socio-demographic data.

	CDH patients	
	N = 42	
Birth	Median	IQrange
Gestational age	38	37–39
Weight at birth	3025	2600–3300
	N	%
Male	31	74
Prenatal Diagnosis	32	76
Fetal Plug	2	5
Pts with Associated anomalies	8	19
Liver in the chest	14	33
First Hospitalization	Median	IQ range
Lenght of hospital stay	30.5	21.3–49.3
Ventilatory Time		
Hours	240	144–504
Days	10	6–21
Number of anesthesia	1	1–1
	N	%
Patch repair	10	24
Sepsis	22	52
At 6 months	Median	IQ range
Days of hospitalization	32	22–53.8
Number anesthesia	1	1–1
At 12 months	Median	IQ range
Days of hospitalization	32	22–53.8
Number of surgeries	1	1–1
Sociodemographic variables	Median	IQ range
Mothers		
Age	33	28–36
	N	%
Italian nationality	34	81
Level of education		
Primary	0	0
Secondary	5	12
High school	29	69
Graduate	8	19
Fathers		
	Median	IQ range
Age	34.5	31–37.3
	N	%
Italian nationality	35	83
Level of education		
Primary	0	0.0
Secondary	10	24
High school	22	52
Graduate	10	24