NEURODEVELOPMENTAL OUTCOME AFTER NEONATAL EXTRACORPOREAL MEMBRANE OXYGENATION

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Abstract • Résumé

Objective: To determine the neurodevelopmental outcome of neonates who underwent extracorporeal membrane oxygenation (ECMO group) and similarly critically ill newborns with a lower Oxygenation Index who underwent conventional treatment (comparison group), and to determine whether factors such as the underlying diagnosis and the distance transported from outlying areas affect outcome.

Design: Multicentre prospective longitudinal comparative outcome study.

Setting: An ECMO centre providing services to all of western Canada and four tertiary care neonatal follow-up clinics.

Subjects: All neonates who received treatment between February 1989 and January 1992 at the Western Canadian Regional ECMO Center and who were alive at 2 years of age; 38 (95%) of the 40 surviving ECMO-treated subjects and 26 (87%) of the 30 surviving comparison subjects were available for follow-up.

Interventions: ECMO or conventional therapy for respiratory failure.

Outcome measures: Neurodevelopmental disability (one or more of cerebral palsy, visual or hearing loss, seizures, severe cognitive disability), and mental and performance developmental indexes of the Bayley Scales of Infant Development.

Results: Six (16%) of the ECMO-treated children had neurodevelopmental disabilities at 2 years of age, as compared with 1 (4%) of the comparison subjects; the difference was not statistically significant. The mean mental developmental index (91.8 [standard deviation (SD) 19.5] v. 100.5 [SD 25.4]) and the mean performance developmental index (87.2 [SD 20.0] v. 96.4 [SD 20.9]) did not differ significantly between the ECMO group and the comparison group respectively. Among the ECMO-treated subjects those whose underlying diagnosis was sepsis had the lowest Bayley indexes, significantly lower than those whose underlying diagnosis was meconium aspiration syndrome. The distance transported did not affect outcome.

Conclusions: Neurodevelopmental disability and delay occurred in both groups. The underlying diagnosis appears to affect outcome, whereas distance transported does not. These findings support early transfer for ECMO of critically ill neonates with respiratory failure who do not respond to conventional treatment. Larger multicentre studies involving long-term follow-up are needed to confirm these findings.

Objectif : Déterminer l'évolution neurologique des nouveau-nés qui ont reçu une oxygénation extracorporelle sur oxygénateur à membrane (groupe OEOM) et celle de nouveau-nés en état critique comparable dont l'indice d'oxygénation était faible, et qui ont reçu un traitement classique (groupe témoin), et déterminer si des facteurs comme le diagnostic sous-jacent et la distance du transport en provenance de régions périphériques modifient les résultats.

Conception : Étude comparative longitudinale prospective et multicentrique des résultats.

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Contexte : Un centre d'OEOM desservant l'ensemble de l'Ouest du Canada et quatre cliniques de suivi néonatal de soins tertiaires.

Sujets : Tous les nouveau-nés traités entre février 1989 et janvier 1992 au Western Canadian Regional ECMO Center et qui étaient vivants à 2 ans; 38 (95 %) des 40 sujets survivants qui ont reçu une OEOM et 26 (87 %) des 30 sujets témoins survivants étaient disponibles pour le suivi.

Interventions : OEOM ou traitement classique de l'insuffisance respiratoire.

Mesures des résultats : Déficience de l'évolution neurologique (un cas ou plus de paralysie cérébrale, de perte de la vue ou de l'ouïe, d'attaques, de déficience grave de la cognition) et indices de développement mental et de performance des échelles Bayley.

Résultats : Six (16 %) des enfants qui ont reçu une OEOM présentaient des déficiences de l'évolution neurologique à l'âge de 2 ans, comparativement à un (4 %) des sujets témoins; l'écart n'était pas important sur le plan statistique. L'indice moyen de développement mental (91,8 [écart type (ET) 19,5] c. 100,5 [ET 25,4]) et l'indice moyen de développement de la performance (87,2 [ET 20,0] c. 96,4 [ET 20,9]) n'étaient pas très différents entre le groupe des sujets qui ont reçu une OEOM et le groupe témoin. Parmi les sujets qui ont reçu une OEOM, ceux chez lesquels on avait diagnostiqué une septicémie présentaient les indices Bayley les plus faibles, de beaucoup inférieurs à ceux chez lesquels on avait diagnostiqué un syndrome d'aspiration de méconium. La distance du transport n'a eu aucun effet sur les résultats.

Conclusions : Il y a eu déficience et retard de l'évolution neurologique chez les deux groupes. Le diagnostic sous-jacent semble avoir un effet sur les résultats, tandis que la distance du transport ne semble pas en avoir. Ces constatations appuient le transfert rapide pour une OEOM des nouveau-nés dont l'état est critique, qui sont en insuffisance respiratoire et qui ne réagissent pas au traitement classique. Pour confirmer ces résultats, des études multicentriques de plus grande envergure comportant un suivi de longue durée s'imposent.

Extracorporeal membrane oxygenation (ECMO) is an accepted form of cardiopulmonary support for neonates of more than 2 kg in weight and 35 weeks or more in gestational age who fail to recover from life-threatening pulmonary illnesses despite conventional medical management.[1-6] This invasive, technically complicated and labour-intensive treatment is a life-support technique that has evolved from refinements in heart–lung bypass technology. Through cannulation of the jugular vein, blood returning to the right atrium is diverted into an extracorporeal circuit, oxygen is added, carbon dioxide is removed, and the blood is then returned into the ascending aorta through cannulation of the common carotid artery (venoarterial) or into the right atrium (venovenous). Thus, the lungs are bypassed for days or weeks while healing occurs. ECMO has been successful in the treatment of neonatal respiratory failure associated with persistent pulmonary hypertension with or without meconium aspiration syndrome, congenital diaphragmatic hernia, sepsis, hyaline membrane disease and other pulmonary conditions including viral lung infection.

The accepted indicator for determining whether respiratory failure is sufficient to begin ECMO is an Oxygenation Index of more than 40 on each of three measurements taken at least 30 minutes apart within a 2-hour window. The Oxygenation Index is calculated according to the following formula.

$$(\text{MAP} \times \text{FiO}_2 \times 100) \div \text{postductal PaO}_2$$

where MAP is the mean airway pressure (in cm H_2O), FiO_2 is the fractional inspired oxygen (in this case it is 1.00 since 100% oxygen is given), and PaO_2 is the partial pressure of oxygen in arterial blood (in torr). The Oxygenation Index reflects both the amount of ventilatory support and the oxygen requirement; the higher the index, the lower the PaO_2. Three measurements taken during a 2-hour window at least 30 minutes apart with values of more than 40 for newborns receiving maximal conventional support predict a mortality of 80%.[1-6] An index of more than 25 but less than 40 predicts a mortality of 50%;[5] this is the level at which transfer to an ECMO centre is recommended.[7]

For neonates ECMO treatment usually lasts 10 days or less. The first successful use of ECMO for neonatal respiratory failure was reported in 1976.[8] The Extracorporeal Life Support Organization Data Registry has detailed records for more than 9000 neonates who have received this therapy.[9] The mortality among infants treated with ECMO has been reversed from 80% or more to 20% or less.[2,5,9] However, a small but significant number of newborns who meet ECMO criteria die before or during transportation.[7]

Since two prospective controlled trials showed a clear benefit for neonatal ECMO over conventional treatment in terms of mortality,[4,10] it has not been possible to evaluate outcome in a randomized controlled trial for ethical reasons. There is a paucity of information about long-term neurodevelopmental outcomes of newborns who have undergone ECMO. Available morbidity data come from individual hospitals and their immediate referral areas. The reported prevalence of neurodevelopmental disabilities, including cerebral palsy, epilepsy, mental retardation and visual or hearing loss, has varied from 10%

to 20% among ECMO-treated survivors.[11–19] Although theoretically ECMO could result in unilateral brain damage, asymmetric neurologic findings have rarely been reported.[11–19] Two recent studies involving 40 and 28 survivors and follow-up of 55% and 60% respectively at 24 and 18 months gave encouraging results, with Bayley scores in the average range although lower than those for healthy term infants in the control groups.[19,20] One preliminary report suggested that the Bayley scores for ECMO-treated subjects are similar to those for concurrent control subjects.[21] The Bayley Scales of Infant Development[22] are the most frequently used tools to provide mental and performance developmental indexes for infants and young children in North America.

There is great interest in the neurodevelopmental outcome of newborns undergoing ECMO, since the procedure involves medical factors that may lead to neurologic complications, particularly cerebral hemorrhage and infarction. These factors include (a) vessel cannulation during hypoxia and often associated hypotension that may interfere with ipsilateral blood flow to the right side of the brain, (b) lack of pulsatile flow, (c) systemic heparinization, (d) exposure of the patient's blood to foreign surfaces, (e) large intravenous catheters and (f) exposure of the patient to large quantities of blood products.[1–3,5,8,23] It has been difficult to separate complications of the underlying disease from those of ECMO.[1] Recently reports of outcome have focused less on these ECMO factors and more on the underlying disease that led to the respiratory failure.[24–27] In addition, the effect on outcome of the distance these critically ill newborns are transported has not been studied.

The objectives of our study were to compare the neurodevelopmental outcomes of neonates who underwent ECMO and neonates in a concurrent comparison group who were referred for ECMO and met all ECMO criteria except the hypoxic criteria but who ultimately received conventional therapy because of a lower Oxygenation Index. In addition, we wanted to evaluate further the role of underlying diagnoses in relation to outcome and to determine whether the distances the neonates were transported affected outcome.

Methods

The design of the follow-up study was that of a prospective longitudinal comparative outcome study. The underlying respiratory diagnoses were determined for all children and the likely primary diagnoses identified.

ECMO centre

The first ECMO program in Canada was established at the Western Canadian Regional ECMO Center early in 1989. This centre, which is at the Royal Alexandra Hospital, Edmonton, provides service to all of western Canada, including the Yukon Territory and the western part of the Northwest Territories, through referrals from tertiary care neonatal intensive care units (NICUs) and is funded by provincial and territorial health dollars. In the first 3 years 93 infants were referred to the centre: 51 received ECMO, 31 received conventional treatment because they did not meet hypoxic ECMO treatment criteria, and 11 (8 from out of province) met all of the ECMO criteria but died either before transportation or before cannulation. Of the 51 infants who underwent ECMO, 40 survived (mortality 22%). All but one of the infants given conventional treatment survived (mortality 3%).

Eligibility criteria

ECMO group

Neonates had to meet all of the following criteria to be eligible for ECMO: birth weight of more than 2 kg; gestational age of 35 weeks or more, confirmed by the mother's dates and findings on physical examination; use of mechanical ventilation for fewer than 10 days; three Oxygenation Index values of more than 40 measured at least 30 minutes apart within a 2-hour window, with an FiO_2 of 1.00 and a mean airway pressure of 18 cm H_2O or greater; no significant signs of structural heart disease on an echocardiogram; no intracranial hemorrhage of grade II or greater; and signed parental consent.

Infants did not receive ECMO if they had a serious life-threatening chromosomal or other abnormality (apart from congenital diaphragmatic hernia) and evidence of severe brain injury incompatible with a normal quality of life (e.g., stage III hypoxic-ischemic encephalopathy[28–30]).

The inclusion and exclusion criteria were not changed during the study period.

Comparison group

Since few neonates who meet the ECMO criteria but do not undergo the procedure survive,[2,5,8] another comparison group of infants with as many features as possible of those of ECMO-treated subjects was needed. Comparison infants were those who met the ECMO treatment criteria and were referred to the ECMO centre but who received conventional treatment because of their lower Oxygenation Index. The following inclusion criteria were determined at the ECMO centre: underlying diagnoses that were the same as those for neonates in the ECMO group; an Oxygenation Index of more than 25 but less than the hypoxic criterion for ECMO treatment on at least two occasions measured at least 30 minutes apart (the FiO_2 and mean airway pressure being the same as those for ECMO-treated subjects) during

mechanical ventilation of at least 48 hours' duration; entry into the same multicentre follow-up program as the ECMO-treated infants; and signed parental consent.

The exclusion criteria were the same as those for the ECMO group.

Neonatal transport

All infants born outside of the ECMO centre were transported by air or road and accompanied by highly skilled neonatal care personnel from the referring NICUs. In each case we obtained the total distance transported (in kilometres) from the sum of distances for each part of the trip, including intra- and intercity and interprovince transfers from primary to secondary or tertiary care NICUs, as applicable.

Baseline information

A neurologic examination was performed at the time of discharge from the ECMO centre's NICU by one of us (C.M.T.R.), who was aware of the subject grouping. Infants with abnormal muscle tone, diminished awareness and abnormal (usually suppressed) primitive reflexes were labelled as having an abnormality, as previously described for term newborns with moderate (stage II) hypoxic-ischemic encephalopathy.[29–31]

A maternal antepartum risk score was calculated for all mothers according to standard format.[32]

In neonatal follow-up in Canada, the Blishen index[33] is a common measure of socioeconomic status. This index, based on Canadian vital statistics, reflects weighted components of education and income level by occupation and indirectly reflects occupational prestige. The father's occupation is usually used because of its value in associated research[29–31] and because more data are available, since more fathers than mothers are employed and mothers are often not employed at the time of the child's birth, when the data are entered into the database. If the father or other major wage earner for the family is unemployed at the time of data entry, the past occupation of the father is used.

To determine the presence of reduced weight for length, as may be found in fetal asymmetric growth restriction associated with placental insufficiency late in pregnancy, we calculated the ponderal index from measurements taken at birth.[34]

Standard post-ECMO computed tomography,[35] and in some cases magnetic resonance imaging, was conducted before hospital discharge.

Outcome measures and follow-up

The outcomes measured were death, regardless of cause, during or following the neonatal period to the time of follow-up at 2 years of age and neurodevelopmental disability or neurodevelopmental dysfunction or delay, as determined at the time of follow-up.

Neurodevelopmental disability was noted if a child had one or more of the following: cerebral palsy (as defined by Bax[36]); visual impairment (corrected visual acuity of less than 6/18 [20/60]) or legal blindness (corrected visual acuity of less than 6/60 [20/200] in the best eye); severe cognitive disability (mental developmental index of more than 3 standard deviations [SD] below the mean on standardized testing[22]); seizure disorder (seizures after the neonatal period necessitating antiepileptic therapy); and neurosensory hearing loss. Functional disability was graded according to the method described by Saigal and associates,[37] with children in the severe category projected to be dependently disabled.

Children who did not have a neurodevelopmental disability but were found to have one or more of the following were considered to have neurodevelopmental dysfunction or delay: moderate cognitive delay (i.e., a mental or psychomotor developmental index of more than 2 SD below the mean on standardized testing[22]) or a language score of more than 2 SD below the mean on standardized testing[38] or indicating at least 6 months' delay for chronologic age.

All of the neonates were prospectively enrolled in the follow-up clinics at the closest (and usually the referring) tertiary care NICU. Multidisciplinary assessments were performed at each of the four follow-up clinic sites. Results were recorded on standard forms forwarded to and checked at the ECMO centre. Every attempt was made to keep those performing the assessments from knowing the subject's group identity. Blinding may have failed if the assessor inadvertently observed the cannulation scar.

The Bayley Scales of Infant Development[22] were chosen as the main standardized outcome measure because they are widely accepted in neonatal follow-up clinics[39] for young children. These scales were applied under the direction of psychologists by qualified psychologists/psychometricians with good reliability scores and experience in using the scales in tests administered to normal and developmentally delayed young children.

The Bayley scales consist of two parts: a mental scale of 163 items that test shape discrimination, sustained attention, purposeful manipulation of objects, imitation and comprehension, vocalization, memory, problem solving and naming of objects, and a motor scale of 81 items that test gross and fine motor skills. The mental developmental index is a good predictor of later childhood intellectual development for children whose index at 2 years of age indicates severe intellectual impairment (less than 50).[40] The revised Bayley scales[41] have normative data for children up to 3½ years of age, but there is substantial overlap in test items with the old version at the 2-year level. The two

scales differ little in the lower range of test scores;[41] thus, the results of our study should be useful for comparisons with those from future studies that use the new scales.

To assess expressive language, the results from the Receptive–Expressive Emergent Language Scale[38] were combined with the speech-language pathologists' or psychologists' observation of language use. All testing was in English, with translation by qualified translators into the family's first language as required.

Statistical analysis

Using a two-tailed test and assuming a Type I error of 0.05 and a power of 0.90, we could determine an effect size of 11 developmental points (two standard errors) of the Bayley mental developmental index with our sample of 38 study and 26 comparison subjects. A power of 0.80 detects effect-size differences in proportions of 25%.

Descriptive statistics for demographic, family, obstetric and neonatal variables were determined for subjects in both groups. Chi-squared tests with Yates' correction were used to test differences between the two groups for noncontinuous variables. For continuous variables, independent *t*-tests and one-way analyses of variance with Scheffé multiple comparisons were used. Pearson product-moment correlations were used to examine relations between variable pairs.

Results

The baseline characteristics did not differ significantly between the two groups except that the ECMO-treated neonates had a lower birth weight and shorter length (although their ponderal indexes were similar to those of the comparison subjects) and a longer stay in the ECMO centre's NICU than the comparison subjects (Table 1). The distance transported varied widely within the two groups, and many newborns had to travel hundreds of kilometres.

The most frequent primary respiratory diagnoses in the ECMO group were meconium aspiration syndrome (including persistent pulmonary hypertension), congenital diaphragmatic hernia and sepsis (Table 2). The incidence of these diagnoses was similar between the two groups except for hyaline membrane disease, which was more common in the comparison group.

Outcome information at 2 years of age was available for 38 (95%) of the 40 ECMO-treated subjects and 26 (87%) of the 30 comparison subjects (Table 3). Of the children lost to follow-up, two in each group were native Indians and moved frequently. As well, two in each group had meconium aspiration syndrome; the other two comparison subjects lost to follow-up had hyaline membrane disease and congenital diaphragmatic hernia respectively. None of the children lost to follow-up had had signs of neurodevelopmental disability at earlier assessments or contacts.

At follow-up 6 (16%) of the 38 ECMO-treated children were found to have neurodevelopmental disabilities, as compared with 1 (4%) of the 26 comparison subjects (Table 3). Two ECMO-treated children had asymmetric neurologic findings: a child with multiple disabilities who had spastic cerebral palsy greater on the left side and a child with hearing loss. None of the children without neurode-

Table 1: Baseline characteristics of neonates undergoing extracorporeal membrane oxygenation (ECMO) and concurrent neonates undergoing conventional treatment (comparison group)

Characteristic	Group; no. (and %) of neonates	
	ECMO *n = 40*	Comparison *n = 30*
Male sex	23 (58)	18 (60)
Both parents as guardians	29 (73)	19 (63)
English as mother tongue	25 (63)	26 (87)
Low antepartum risk score[32]	28 (70)	19 (63)
Vertex vaginal delivery	23 (58)	19 (63)
Singleton birth	39 (98)	29 (97)
Birth at ECMO centre	2 (5)	4 (13)
Apgar score ≤ 3 at 1 minute	18 (45)	6 (20)
Apgar score ≤ 3 at 5 minutes	4 (10)	0
Neonatal convulsions	8 (20)	4 (13)
Normal findings on neurologic examination at discharge from NICU*	10 (25)	14 (47)
Normal findings on cranial imaging†	34 (85)	29 (97)
	Mean (and SD)	
Father's socioeconomic status, Blishen index[33]	39.1 (17.1)	43.4 (20.9)
Maternal age, yr	26.0 (5.7)	26.0 (5.2)
Maternal schooling, grade	12.4 (2.7)	13.0 (2.9)
Maternal gravida	2.4 (1.3)	2.3 (1.2)
Gestational age, wk	39.2 (2.2)	38.7 (1.9)
Ponderal growth index[34]	2.4 (0.4)	2.5 (0.3)
Birth weight, kg	3.0 (5.9)	3.4 (5.0)‡
Length at birth, cm	49.7 (2.2)	52.4 (2.4)§
Head circumference at birth, cm	34.5 (1.6)	35.2 (1.3)
Length of stay in NICU, d	47.8 (41.7)	22.4 (15.4)§
Distance transported, km	580 (555)	463 (459)

*NICU = neonatal intensive care unit.
†Computed tomography and magnetic resonance imaging.
‡$p = 0.002$.
§$p \leq 0.001$.

Table 2: Underlying primary respiratory diagnoses

Diagnosis	Group; no. (and %) of neonates: ECMO *n = 40*	Comparison *n = 30*
Congenital diaphragmatic hernia	8 (20)	3 (10)
Hyaline membrane disease	2 (5)	9 (30)*
Hypoplastic lung	1 (3)	0
Lung mass	1 (3)	0
Meconium aspiration syndrome	19 (48)	12 (40)
Persistent pulmonary hypertension	3 (8)	2 (7)
Sepsis	4 (10)	4 (13)
Viral lung infection	2 (5)	0

*$p = 0.02$.

Table 3: Neurodevelopmental outcome at 2-year follow-up

Outcome	Group; no. (and %) of subjects*: ECMO *n = 38*	Comparison *n = 26*
Neurodevelopmental disability		
Disabled	6 (16)	1 (4)
Cerebral palsy	2 (5)	1 (4)
Spastic quadriplegia	1	1
Spastic bilateral hemiplegia (greater on left side)	1	0
Hearing loss	3 (8)	0
Severe cognitive disability†	2 (5)	1 (4)
Seizures requiring antiepileptics	1 (3)	1 (4)
Vision loss	3 (8)	1 (4)
Visual impairment	3	0
Legal blindness	0	1
Two or more disabilities	3 (8)	1 (4)
Projected to be dependently disabled	2 (5)	1 (4)
Neurodevelopmental delay		
Expressive language delay[38]	7 (18)	3 (12)
Moderate cognitive delay‡	2 (5)	0
Bayley developmental indexes[22]		
Mental index, mean (and SD)§	91.8 (19.5)	100.5 (25.4)
Performance index, mean (and SD)§	87.2 (20.0)	96.4 (20.9)

*Unless otherwise stated.
†More than 3 SD below the mean.[22]
‡Two to 3 SD below the mean.[22]
§Normative data = mean 100 (SD 16).[22]

velopmental disabilities were noted to have asymmetric findings. Of the three ECMO-treated children with neurosensory hearing loss, one had moderate loss at low frequencies and severe loss at frequencies in the middle to high range. The other two had normal hearing at low frequencies and severe hearing loss at high frequencies; hearing loss was first noted at frequencies greater than 1000 Hz in one case and greater than 2000 Hz in the other. All of these three children required amplification devices for language development and education. Three of the ECMO-treated children had visual impairment, the cause of which was central, with one child having severe cognitive delay as well as bilateral optic nerve hypoplasia without signs of congenital central-nervous-system abnormalities on imaging. Although not shown in Table 3, the distances transported did not differ significantly between the subjects with neurodevelopmental disabilities and those without. In the two groups the mean mental and performance developmental indexes of the Bayley scales were within the average range of normative data. The indexes did not differ significantly between the two groups even when children with neurodevelopmental disabilities were excluded.

The relation between the primary respiratory diagnoses and the incidence of neurodevelopmental disabilities, the mean Bayley indexes and the distance transported for the 38 ECMO-treated infants are given in Table 4. The neonates who had undergone ECMO because of sepsis-related respiratory failure had the most adverse outcome, with significantly lower Bayley indexes than those of the subjects who had undergone ECMO because of meconium aspiration syndrome. In the ECMO group, there was no significant correlation between the developmental indexes and either the general demographic characteristics or the distances transported.

Discussion

The rates of death (22% [11/51]) and of neurodevelopmental disability (16% [6/38]) among the ECMO-treated infants in our study were similar to those previously reported.[1-3,9,11-19] Some neonates who met the ECMO treatment criteria died before transfer or cannulation, which accounts for what have been called "hidden deaths."[7] Nevertheless, 25 (66%) of the 38 ECMO survivors assessed at 2 years of age did not have a neurodevelopmental disability or delay as defined by our criteria.

The proportion of children with neurodevelopmental disabilities at follow-up and the Bayley indexes did not differ significantly between the two groups. Of the 32 ECMO-treated children without neurodevelopmental disabilities 7 (22%) had an expressive language delay; however, this proportion did not differ significantly from that in the comparison group. A concern about language development has been previously raised.[19] Our finding that the

ECMO survivors with an underlying diagnosis of meconium aspiration syndrome had higher developmental indexes than those whose underlying diagnosis was sepsis supports the suggestion that the underlying diagnosis necessitating ECMO is a good predictor of outcome.[27] Distance travelled and socioeconomic status were not found to be good predictors of neurodevelopmental outcome.

Although our findings are similar to those of a recent study involving ECMO-treated survivors followed up at 2 years of age[19] we covered a much greater geographic area and considered hidden mortality and distance travelled in addition to mortality, neurodevelopmental disability and neurodevelopmental outcome indexes. The proportion of infants available for follow-up exceeded that reported in most other outcome studies. The follow-up period was the same for each subject, which allowed us to use one developmental test rather than several tests for various age groups. In addition, the follow-up was by multidisciplinary assessment, not by letter or telephone interview.

More than 150 neonates have undergone ECMO in Canada, at three centres (in Montreal, Toronto and Edmonton); however, less than one third of them are 2 years of age or older. This is the first study of neurodevelopmental outcome after neonatal ECMO in Canada. It is unique because of the high proportion of survivors assessed at 2 years of age, the inclusion of a concurrent comparison group of referred newborns who were successfully treated without ECMO, and the analysis of distance travelled.

We believe that our results are important for all physicians practising obstetrics or providing neonatal care. A severely ill neonate with respiratory failure may be delivered at any location. It is only through knowledge of available treatments that parents can be informed of options in an expedient manner and thus leave sufficient time for transportation of the neonate to an ECMO centre. We believe that for most neonates who meet the eligibility criteria outlined in our study, ECMO is associated with an acceptably low risk of adverse outcome, regardless of the transportation distance required.

The limitation of this study was a sample size that had adequate power to detect medium and large effect-size differences but not smaller ones. Given the standard errors of the Bayley scales upon which the needed effect sizes were based, this study had adequate power to detect meaningful differences in the developmental indexes between the two groups. Comparisons between the two groups according to underlying diagnoses were completed by analysis of variance because of the low numbers of subjects in the subgroups. Our findings could theoretically be strengthened by the fact that the subjects in the comparison group were larger at birth, had better Oxygenation Indexes and had shorter stays in the NICU than those in the ECMO group, yet they did not appear to have significantly better outcomes.

Our findings add to the current information on the effectiveness and safety of ECMO and associated health care support systems. They further delineate the role of the underlying diagnosis in predicting neurodevelopmental outcome after ECMO. Further long-term follow-up to evaluate memory, reasoning, behaviour, sound discrimination and sequencing of auditory information, attention, language and neuromotor outcome for this group of high-risk children is being planned.

We thank all the parents who travelled long distances to provide follow-up information for our study and the dedicated specialists who assessed the children.

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Table 4: Relation of primary underlying diagnoses of ECMO-treated subjects to neurodevelopmental outcome at 2 years of age and distance transported

Variable	Underlying diagnosis* MAS/PPH *n = 20*	Sepsis *n = 4*	CDH *n = 8*	Other *n = 6*	*p* value
No. (and %) of children with neurodevelopmental disability	1 (5)	2 (50)	2 (25)	1 (17)	0.123†
Mean mental developmental index	100	63‡	87	90	0.002§
Mean performance developmental index	96	64‡	83	77	0.006§
Mean distance transported, km	427	206	931	921	0.106§

*MAS/PPH = meconium aspiration syndrome/persistent pulmonary hypertension, CDH = congenital diaphragmatic hernia.
†One-way analysis of variance with Scheffé multiple comparisons.
‡Significantly lower than index for ECMO-treated children with MAS/PPH.
§Chi-squared test for independent proportions.

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