The long-term outcome of children managed with extracorporeal life support: an institutional experience

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ABSTRACT

Objective: To evaluate the long-term functional status and quality of life of infants and children who have received extracorporeal life support (ECLS), and to determine how and when death occurred.

Design: Long-term, prospective follow-up study.

Setting: 16-bed paediatric intensive care unit in a university teaching hospital.

Participants: All children who received ECLS in the period April 1988 to October 2000 in the paediatric ICU at the Royal Children's Hospital, Melbourne, VIC.

Methods: The records of all 224 children who had received ECLS were reviewed, and functional status and quality of life were assessed through interview with each child's parent or guardian for those who had survived.

Results: Follow-up information was available for 211 children at a median of 7.2 years (range, 3.9 months to 12.6 years) after admission to the paediatric ICU. Sixty-nine children were alive at follow-up, 96% of whom were likely to lead an independent existence. Of the 142 deaths, 123 occurred in the paediatric ICU: 74 were due to elective withdrawal of therapy for poor prognosis, and eight for brain death; 30 were disease-related; seven were ECLS-related; and four were due to sepsis.

Conclusions: ECLS is a complex therapy which has been used in Australian children for 18 years; a third of children survived long term, and 96% of these had a favourable outcome.

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Extracorporeal life support (ECLS) is now recognised in many countries as standard therapy for the supportive management of children with severe, life-threatening respiratory and circulatory failure. Because of the small number of children who require ECLS and the complexity of care associated with this service, it is offered by only three paediatric intensive care units in Australia. The ECLS program at the Royal Children's Hospital, Melbourne, Victoria, commenced in 1988 for infants and children with acute, potentially reversible respiratory and/or circulatory failure.

Improved survival of infants and children managed with ECLS has been well documented,[1-9] with an overall survival to ICU discharge of 65% in a cohort of 32 905 patients who received extracorporeal membrane oxygenation (report of the Extracorporeal Life Support Organization, July 2006[10]). However, the severity of illness of children who receive ECLS, and the inherent risks associated with the procedure, including bleeding, cerebrovascular embolism and infection,[10] may all contribute to patient outcome. To evaluate the true efficacy of ECLS, it is therefore essential to determine whether the improved survival of children who have received ECLS has occurred at the expense of their long-term function and quality of life.[11]

The published functional outcomes of infants and children treated with ECLS vary markedly, mainly because of differences in diagnoses, timing of outcome assessment and attitudes to withdrawal of treatment. The most favourable outcomes have been obtained in neonates with an acute, severe respiratory illness (excluding congenital diaphragmatic hernia). Outcome has largely been assessed at ICU or hospital discharge, with 90% of infants surviving.[12] However, functional outcome assessment at 1 to 7 years following ECLS has shown that favourable neurological outcomes occur in 33% to 65% of surviving infants.[13-15] In contrast, among neonates with congenital diaphragmatic hernia, only 10% have favourable outcomes — normal or mild functional impairment — apparent at 1 year.[16] Infants and children receiving ECLS for cardiac disease have demonstrated favourable functional outcomes in only 12% to 23% of children when assessed at 1–4 years after ECLS.[17-19]

The purpose of this study was to identify the long-term outcome of all infants and children managed with ECLS at the Royal Children's Hospital, Melbourne, since commencement of the program in 1988.

Methods

All children who received ECLS in the ICU at the Royal Children's Hospital, Melbourne, between April 1988 and 31 October 2000 were included in the study.

Hospital data collection

Data were collected prospectively to assess the condition of children before the commencement of ECLS, including principal admission diagnosis (classified as neonatal, congenital diaphragmatic hernia, paediatric lung disease, cardiac [neonatal and paediatric], and sepsis), documentation of a cardiac arrest (defined by the performance of external

cardiac massage), use of high frequency oscillatory ventilation (HFOV) and nitric oxide therapy.

Severity of illness was evaluated through calculation of an oxygen index (mean airway pressure × F_{IO_2}/Pa_{O_2} × 1000), ventilation index (P_{CO_2} [mmHg] × respiratory rate × peak inspiratory pressure/1000) and inotrope score ([dopamine dose {μg/kg/min}] + [dobutamine dose {μg/kg/min}] + [20 × adrenaline dose {μg/kg/min}] + [20 × noradrenaline dose {μg/kg/min}] + [25 × 10% calcium gluconate dose {mL/kg/h}] + [10 000 × vasopressin dose {U/kg/min}]).

Data were collected in accordance with the guidelines of the Extracorporeal Life Support Organization registry, including age at commencement of ECLS, reason for ECLS, type(s) and duration of support required, place of vascular cannulation, and, during the period of ECLS, the frequency of physiological abnormalities and mechanical malfunction. Reason for ECLS was classified as severe lung disease, acute deterioration, barotrauma, failure to respond to maximum therapy, transpulmonary shunt, circulatory failure (cardiac shock or cardiac arrest), inability to wean from cardiopulmonary bypass, and bridge to transplantation. Length of stay in the ICU was also recorded.

Outcome evaluation

Using a standardised questionnaire,[18] outcome status was evaluated through telephone interview with each child's parent or guardian by the nursing ECLS coordinator (R C), under the supervision of a research coordinator experienced in outcome evaluation and independent of the ECLS team (A K T). Children who had reached adulthood at the time of outcome assessment and were living independently were interviewed directly.

We used the Paediatric Overall Performance Category Scale (POPC)[19] to assess overall functional outcome. Outcome categories for the POPC score were defined as: good overall performance (healthy, alert and capable of normal activities of daily life); mild overall disability (possibility of minor physical problem that is still compatible with normal life; conscious and able to function independently); moderate overall disability (possibility of moderate disability from non-cerebral system dysfunction alone or with cerebral system dysfunction; conscious and performs independent activities of daily life but is disabled for competitive performance in school); severe overall disability (possibility of severe disability from non-cerebral systems dysfunction alone or with cerebral system dysfunction; conscious but dependent on others for activities of daily living support); coma or vegetative state and brain death. Children who survived with good overall performance or mild or moderate overall disability were considered to have a favourable outcome, while those who survived with a severe overall disability or in a vegetative state were regarded as having an unfavourable outcome. The latter categorisation was based on a distinction between children who survive as functionally independent (albeit with significant problems) and those who are dependent on the care of others for activities of daily living; this categorisation is consistent with that used in other outcome-based studies conducted at our hospital.[20]

In children who were aged 1 month or more at the time of commencement of ECLS, the presence of comorbidities was recorded following retrospective review of patient records. Pre-existing health status was then classified using the POPC. The nature of disability was classified as motor, cognitive, behavioural or cardiorespiratory.

We assessed quality of life using the Health State Utility (HSU) Index, Mark 1.[21] The HSU Index comprises four categories, each representing possible levels of functioning with respect to physical function (mobility and physical activity), role function (self care and role activity), social and emotional function (emotional and social activity), and health problems. All levels within each category are assigned a numerical value, from which an overall HSU value is calculated. All possible health states lie within a range of 1.00 to –0.21, where 1.00 is healthy, 0 is dead, and negative values reflect a health state considered "worse than death".[21] Four outcome categories were assigned: good (HSU, 1.00–0.7); moderate (HSU, 0.69–0.3); poor (HSU, 0.29–0); and very poor (HSU < 0). Good was considered a favourable outcome, while categories moderate, poor and very poor were considered unfavourable. This categorisation is consistent with that used in other outcome-based studies conducted at our hospital.[20]

Cause of death was classified as disease-related, ECLS-related or elective discontinuation of treatment for brain death or poor prognosis. Brain death was diagnosed according to standard criteria.[22] Timing of death in relation to vascular decannulation was noted.

Ethics approval for the study was obtained from the Hospital's Ethics in Human Research Committee. All patient data were collected and stored in accordance with current privacy legislation and guidelines. Descriptive analysis of the data was performed using Stata release 7.0 (StataCorp, College Station, Tex, USA).

Results

Two hundred and twenty-four children, accounting for 225 episodes of care, received ECLS between 1 April 1988 and 31 October 2000. One child was admitted to the ICU on two separate occasions and required ECLS during both admissions. One hundred and sixteen children aged 1 month or more at the time of commencement of ECLS were evaluated for the presence of pre-existing abnormality: 48

Table 1. Severity of illness in children before commencement of extracorporeal life support, by primary admission diagnosis ($n = 225$)

Diagnostic group	Oxygen index median (range)*	Ventilation index median (range)*	Inotrope score median (range)*	Number with		
				Cardiac arrest	Nitric oxide therapy	HFOV
Neonatal ($n = 39$)	703 (5.1–137.5)	79.2 (16.7–342)	15 (5–68.8)	5	8	9
Congenital diaphragmatic hernia ($n = 20$)	71.3 (28.6–189.2)	170.0 (122.4–361.8)	17.8 (5–70)	1	8	9
Paediatric lung disease ($n = 28$)	55.1 (20.2–83)	59.5 (35–110.3)	13.5 (5–92)	7	5	4
Cardiac neonatal/paediatric ($n = 112$)	7.1 (0.6–60.6)	18.0 (8.5–64.2)	17.0 (4–95)	28	6	0
Sepsis ($n = 26$)	35.9 (2.1–69.2)	40.6 (10.6–96.8)	31 (2–285.8)	14	2	3

* See text for definitions. HFOV = high frequency oscillatory ventilation.

(41%) had a good overall performance, 65 (56%) had a mild overall disability, and three (3%) had a moderate overall disability. No child with a severe overall disability or who was in a vegetative state received ECLS. The severity of illness of children before the commencement of ECLS is shown in Table 1.

The median age of the children at commencement of ECLS was 1.5 months (range, 1 day to 20 years). In 102 (45.3%) cases, ECLS was required in infants less than 1 month of age. Cannulation was performed in the operating theatre on 75 (33.3%) occasions and in the ICU in 150 (66.7%) cases. Extracorporeal membrane oxygenation (ECMO) was used on 169 occasions, a veno-arterial technique on 146 occasions, and a veno-venous technique on 27. Left ventricular assist was required on 69 occasions, right ventricular assist on one occasion, and biventricular assist on two occasions. Twenty children received two types of ECLS on separate occasions: ECMO and ventricular assist in 15 cases; and veno-venous and veno-arterial ECMO in four cases. In each of these children, there was conversion from one mode to another, so that each child was always receiving one form of ECLS. One child received both left ventricular assist and subsequent biventricular assist. The median duration of extracorporeal life support was 94 hours (range, 2 hours to 52.9 days). The median stay in the ICU was 216 hours (9 days) (range, 9 hours to 112 days).

Outcomes

Follow-up information was available for 211 children (94.2%); international and some interstate patients could not be contacted. Outcome was evaluated at a median of 7.2 years (range, 3.9 months to 12.6 years) after admission to the paediatric ICU. The median age of children at the time of outcome assessment was 8.5 years (range, 14 months to 26 years).

Of the 211 children evaluated, 69 (32.7%) were alive at the time of follow-up, while 142 (67.3%) had died. Outcome status for the 69 survivors was favourable using the POPC scale in 66 children (96%) who were likely to lead an independent existence: good overall performance in 42 (61%), mild overall disability in 15 (22%), and moderate overall disability in nine (13%). Three children (4%) had an unfavourable outcome (severe overall disability) and were likely to survive dependent on care by others for activities of daily living. According to the HSU index, 49 children (71%) survived with a good quality of life, 16 (23%) with a moderate quality of life, and four (6%) with a poor quality of life. No child survived with a very poor quality of life. Twenty-seven (39%) children survived with a disability: motor disabilities in 14, cognitive disabilities in six, behavioural disabilities in two, and cardiorespiratory disabilities in 11. Six children survived with more than one disability.

Ninety-five infants who were available for follow-up commenced ECLS before 1 month of age: 35 (37%) survived, of whom 34 (97%) had a favourable outcome (good overall performance in 24, mild overall disability in 6, and moderate overall disability in 4) and one (3%) had an unfavourable outcome (severe overall disability). One hundred and sixteen children commenced ECLS at 1 month of age or older: 34 (29%) survived, of whom 32 (94%) had a favourable outcome (good overall performance in 18, mild overall disability in 9, and moderate overall disability in 5), and two children (6%) had an unfavourable outcome (severe overall disability).

The relationship between primary admission diagnosis (by group) and long-term outcome is shown in Table 2. The relationship between reason for ECLS and long-term outcome is shown in Table 3.

Of the 142 children who died, 123 (86.6%) died during their admission to the ICU, 93 during ECLS, eight within 48 hours of decannulation, eight between 48 and 168 hours after decannulation and 14 more than 7 days after decannulation. Eight children died following discharge to the hospital ward, and 11 died following discharge from

Table 2. Long-term outcome of children receiving extracorporeal life support (ECLS), by primary admission diagnosis (*n* = 211)

Diagnostic group	Good	Mild disability	Moderate disability	Severe disability	Vegetative state	Dead
Neonatal (*n* = 34)	14	2	1	1	0	16
Congenital diaphragmatic hernia (*n* = 20)	3	1	1	0	0	15
Paediatric lung disease (*n* = 27)	5	6	1	1	0	14
Cardiac neonatal/paediatric (*n* = 105)	16	3	4	1	0	81
Sepsis (*n* = 25)	4	3	2	0	0	16

Table 3. Long-term outcome of children receiving extracorporeal life support (ECLS), by reason for ECLS (*n* = 211)

Reason for ECLS	Good	Mild disability	Moderate disability	Severe disability	Vegetative state	Dead
Severe lung disease (*n* = 114)	29	9	5	1	0	70
Circulatory failure (*n* = 42)	5	5	2	1	0	29
Unable to wean from cardiopulmonary bypass (*n* = 54)	7	1	2	1	0	43
Bridge to transplantation (*n* = 1)	1	0	0	0	0	0

hospital for the studied admission. Of the 123 children who died in the ICU, cause of death was identified as disease-related (30), ECLS-related (7) and sepsis (4), while treatment was electively discontinued for poor prognosis (74) and brain death (8). In the 19 children who died outside the ICU, cause of death was disease-related (13), respiratory collapse (2), elective discontinuation of treatment for poor prognosis (1) and sepsis (1), and could not be established in two.

Discussion

The long-term survival of infants and children managed with ECLS in our institution was 32.7%, with 96% of those who survived having a favourable functional outcome. Only 4% of children had an unfavourable outcome and were likely to be dependent on care by others for activities of daily living. This compares favourably with the published outcomes of other ECLS programs, summarised in Table 4.

The results of all ECLS events worldwide are recorded by the Extracorporeal Life Support Organization. The July 2006 report[10] indicated that 23 620 newborn infants and 7241 children had ever received ECLS; 71.5% of newborns and 49.1% of children survived to the time of return transfer to their referring hospital or discharge from the paediatric or neonatal ICU of the ECLS centre. While individual ECLS centres have widely published their results for survival and longer term outcomes of newborns having ECLS,[23] there is only now some literature on longer term outcomes of older children.[12-17,24-32] When comparing our overall results with those of other centres, it is important to remember that patient outcome is influenced by many factors, including underlying diagnosis and severity of illness, institutional criteria relating to the eligibility and timing of ECLS, the time at which outcome status is evaluated, and, most importantly, attitudes of family and staff to discontinue therapy in the face of poor predicted long-term outcome. These factors are essential to understanding the differences in published ECLS outcomes.

In our hospital, ECLS is often used in emergency situations in an attempt to resuscitate and stabilise the most critically ill infants and children. In these situations, a decision is made 2–3 days after commencement of this therapy as to whether to continue. Any concerns regarding potential neurological impairment prompt measurement of somatosensory evoked potentials[33-35] and cerebral computed axial tomography. This enables early decisions to be made about long-term prognosis. This philosophy has provided information to parents and has underpinned our high rate of elective discontinuation of therapy, and consequent high rate of favourable functional outcomes among survivors; interestingly, our percentage of independent outcomes, when adjusted for diagnosis, is similar to that of other centres (Table 4).

There appears to be a relationship between the long-term outcome of children managed with ECLS and primary admission diagnosis (Table 2). Newborn infants with respiratory disease had a favourable long-term outcome in 50% of cases and a 47% mortality rate, while among those with congenital diaphragmatic hernia, 25% had a favourable outcome, and 75% died. Clearly, pulmonary hypoplasia is not optimally managed by ECLS. Children with respiratory

Table 4. Other published studies of outcome of extracorporeal life support in infants and children

Study	Diagnosis	Number	Alive (%)	Time to follow-up (years)	Normal or mild to moderate disability (%)
Kugelman 2005	Meconium aspiration syndrome	126	94%	Discharge	Unknown
Khambekar 2006	Neonatal	145	75%	1	65%
Jaillard 2000	Neonatal	57	63%–70%	2	53%–60%
United Kingdom Trial 1998	Neonatal	93	68%	1	53%
Petrou 2006	Neonatal	93	55.4%	7	33%
Davis 2004	Congenital diaphragmatic hernia	73	27%	1	9.6%
Nield 2000	General (neonatal)	322	81%	3.5	48%
Amigoni 2005	General	36	58%	9	47%
Van Listenburg 2005	ARDS	80	39%	1	25%
Mahle 2005	Rescue	32	47%	1	< 37%
de Mos 2006	Cardiac arrest	91	23%	1	< 19%
Ibrahim 2000	Cardiac	67	37%	3	12%
Chen 2003	Cardiac	57	32%	1	28%
Morris 2004	Cardiac	66	32%	Discharge	24%
Hamrick 2003	Cardiac	53	26%	4	13%

ARDS = acute respiratory distress syndrome.

failure had a favourable outcome in 44% of cases, but 52% died. Sepsis was associated with 64% mortality, and only 36% of children achieved a favourable long-term outcome. ECLS is clearly useful as short-term support in children with cardiac abnormalities, but, from a structural perspective, a severely abnormal heart defines the limitations of ECLS in this group and underpins long-term outcome, with only 22% of infants and children having a favourable outcome, and 77% dying. This needs to be appreciated when reviewing the results of other international ECLS centres with different case mix.

The reason for ECLS is important to the potential outcome (Table 3). Severe lung disease, which has well established predictors of mortality in our ICU,[36] was associated with the best outcome: 61% mortality, and a favourable outcome in 38% of infants and children. Circulatory failure, which has more poorly defined criteria underlying the use of ECLS, was associated with 69% mortality, and a favourable outcome in 29% of children. Failure to wean from cardiopulmonary bypass was associated with the worst outcome, with 80% mortality, and only 19% of children achieving a favourable outcome.

ECLS provides a period of rest to the lungs and/or heart, limiting iatrogenic lung and cardiac injury while maintaining cardiac output and tissue oxygenation. Maximum organ recovery in the presence of potentially reversible disease is therefore promoted. From this perspective, ECLS is a supportive rather than curative therapy. While ECLS may, in combination with optimal intensive care, assist in the recovery from an acute, life-threatening episode of illness, the residual sequelae of the underlying disease process and its management may persist for many months or years, affecting a child's global functioning and quality of life.

Conclusions

Ninety-six per cent of long-term survivors of ECLS have a good outcome. Elective withdrawal of treatment because of poor prognosis is an important consideration when using this therapy. As large-scale, randomised controlled trials are not currently possible, continued long-term follow-up is essential for evaluation of this therapy.

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