Follow-up of children who received complex invasive therapies early in life

Reg Sauve MD MPH FRCPC[1], Charlene MT Robertson MD FRCPC[2]

R Sauve, CMT Robertson. Follow-up of children who received complex invasive therapies early in life. Paediatr Child Health 2006;11(5):287-290.

The present article reviews existing literature and outcome assessment processes used in programs that provide various complex paediatric therapies. The published literature is summarized, and enrolment and assessment details used in the Complex Paediatric Therapies Registry in the province of Alberta are discussed. Several studies have reported the outcomes of infants and children who received various complex invasive therapies. Four hundred eighty-three infants and children who received specific complex therapies in Alberta and survived to discharge were enrolled in neonatal follow-up programs in their home provinces. Compliance rates are 96% or higher at baseline, 18 months and four years of age. In general, cerebral palsy, blindness and deafness are very rare, but developmental delay and borderline cognitive function are more frequent. Analysis of the predictors of the adverse outcomes of such infants has permitted optimal parent counselling and initiation of efforts to improve outcomes.

Key Words: *Follow-up; Life-saving paediatric therapies; Outcomes*

Le suivi des enfants qui reçoivent des traitements effractifs complexes en début de vie

Le présent article contient l'analyse des publications et des processus d'évaluation des issues utilisés dans les programmes qui proposent diverses thérapies pédiatriques complexes. Les publications sont résumées et le détail du recrutement et de l'évaluation utilisé dans le *Complex Paediatric Therapies Registry* de la province de l'Alberta est exposé. Plusieurs études font état du sort des nourrissons et des enfants qui ont reçu divers traitements effractifs complexes. Quatre cent quatre-vingt-trois nourrissons et enfants qui avaient reçu un traitement complexe en Alberta et qui ont survécu jusqu'au congé ont été recrutés dans les programmes de suivi néonatal de leur province de naissance. Les taux d'observance sont d'au moins 96 % au départ, à 18 mois et à quatre ans. En général, l'infirmité motrice cérébrale, la cécité et la surdité sont très rares, mais les retards de développement et les fonctions cognitives limites sont plus fréquents. L'analyse des prédicteurs d'issues indésirables chez ces nourrissons permet d'offrir des conseils optimaux aux parents et d'entreprendre des efforts pour améliorer le sort de ces enfants.

As newly emerging health technologies develop and are used in the treatment of life-threatening illnesses in young children, gaps in our understanding of the long-term outcomes of infants and children receiving these therapies become obvious. Infants and young children who undergo complex paediatric therapies, such as open heart surgery (1-5), extracorporeal membrane oxygenation (ECMO) (6-9) and solid organ transplants (10-14), are at risk for adverse long-term outcomes. The risk factors associated with adverse outcomes are multifactorial. For some children, the risk factors are associated with the critical illness necessitating the treatment, while in others, the risk factors are more specifically linked to the invasive therapy required. In addition, congenital abnormalities, as found in some of these children, are linked not only with the condition that necessitated the complex therapy and its treatment, but also with the long-term neurodevelopmental outcome.

The rare, technically demanding procedures of interest here, such as open heart surgery in small infants, ECMO and solid organ transplants, are generally done in centres where there is the greatest likelihood of success. These are often high-volume centres with state-of-the-art infant transport, preoperative diagnostic capabilities and support, operative techniques and postoperative management capabilities (5). The risk status of these young children has been recognized for some time, but parents of young children needing life-saving treatments could be offered little information beyond survival statistics. Knowledge about patterns of health and neurodevelopmental outcomes after these therapies is just beginning to emerge. A number of reports (1-5) on outcomes of open heart surgery in small infants have been published, and there has been a plea for centres treating congenital heart disease to collect and analyze outcome data, and to make these available to families with affected children and other institutions (5). There are also some data on the outcomes of infants and children treated with ECMO (6-9) and those with solid organ transplants (10-14), but many unanswered questions remain, and the same plea can be made to centres providing these therapies.

Recently, developments in the structure and processes of neonatal follow-up programs, and linkages between these and the programs providing complex paediatric therapies,

[1]*Departments of Pediatrics and Community Health Sciences, University of Calgary, and Alberta Children's Hospital, Calgary;*
[2]*Department of Pediatrics, University of Alberta, and Glenrose Rehabilitation Hospital, Edmonton, Alberta*
Correspondence: Dr Charlene Robertson, Glenrose Rehabilitation Hospital, 10230 – 111th Avenue, Edmonton, Alberta T5G 0B7. Telephone 780-735-7999 ext 15426, fax 780-735-7907, e-mail croberts@cha.ab.ca

have provided novel follow-up opportunities (3). By expanding the boundaries of neonatal follow-up programs to include infants whose risk status is determined by 'new' or incompletely studied invasive therapies for life-threatening conditions rather than exclusively by preterm birth and hypoxic-ischemic encephalopathy, opportunities have been created to include these infants in longitudinal, multidisciplinary neonatal follow-up programs. Existing neonatal follow-up programs have the framework, experience and expertise to initiate long-term follow-up for such infants (15). These children and their families can benefit from the advantages of multidisciplinary follow-up, and analyses of specific factors associated with adverse outcomes can set the stage for supporting or modifying care approaches for future children.

RELATED WORK

Several reports have described mechanisms through which neurodevelopmental abnormalities may occur in infants with serious cardiac defects that require early surgical intervention. For example, du Plessis (16) and others (17,18) have described potential mechanisms of the brain damage that occurs during the preoperative, operative and postoperative periods of infant cardiac surgery. The preoperative mechanisms include chromosomal and dysgenetic factors, and injuries acquired during early periods of cardiorespiratory instability. Cerebrovascular incidents described during surgery led to hypoxic-ischemic and reperfusion injury, cerebral embolism, cerebral inflammatory microcoagulopathy or microvascular occlusion. The registry and follow-up of the Western Canadian Complex Pediatric Therapies Project (3) reported that the risk of an adverse outcome was cumulative, with preoperative and potentially modifiable operative determinants making significant contributions. Fifty-five per cent of the outcome variance was explained by the duration of preoperative ventilation, and the remainder was explained by genetic anomalies, or intraoperative or postoperative variables (3).

Children with hypoplastic left heart syndrome and those with underlying chromosomal defects were reported to have the highest rates of long-term morbidity in a group of infants with congenital heart disease, although 43 of 67 children (43%) in the total group were considered 'intact' (3). The Boston Circulatory Arrest Study Group (19) has contributed important results on the outcomes of infants with d-transposition of the great arteries who were enrolled in a randomized controlled trial of deep hypothermic circulatory arrest versus low-flow cardiopulmonary bypass. In early assessments, the children had IQ scores somewhat below population means, but they were closer to normal at eight years of age. Significant defects in visual-spatial and complex operations were also evident.

Some reports (6-9) from clinical trials and case studies have documented the long-term outcomes of infants and children who received ECMO. ECMO may be required independently or as a component of open heart surgery; different outcomes may be anticipated in the two treatment groups. Hypoxia and ischemia present before the ECMO, reperfusion injury, impaired cerebral perfusion and other factors may lead to long-term morbidity in survivors. Infants who required ECMO due to congenital diaphragmatic hernia have been noted to be at particular risk of long-term neurodevelopmental abnormalities (9).

Long-term follow-up studies of infants and young children following solid organ transplants (heart, liver or kidney) are somewhat limited. The anticipated long-term morbidity varies according to the type of transplant; the child's health status before the transplant; the underlying disease; and, possibly, details of the preoperative, operative and postoperative management. Studies (10-14) have described relatively frequent cognitive and growth deficits in some populations of children who received liver transplants. Academic outcomes were reported as suboptimal in a substantial proportion of liver transplant recipients, and ongoing psychological and educational support have been recommended (12,13). Children with end-stage renal failure are known to have poor brain growth and developmental delay (20). The impact of early dialysis and renal transplantation on long-term outcome is not clear. There have been reports (10,11) of generally good developmental outcomes in children who had renal transplants, but this is less common with long-term dialysis and early onset of renal failure.

OUR APPROACH

Building on experience and on the linkages developed during preliminary studies of the outcomes of populations of preterm infants, those with hypoxic-ischemic encephalopathy and those with congenital cardiac anomalies, we developed a multisite, interprovincial follow-up program to provide longitudinal outcome assessments of broader groups of infants who received complex paediatric therapies in the province of Alberta (3). The infants and children enrolled in the program had conditions that were considered to require newly emerging or incompletely studied technologies, and were at particular risk of an adverse outcome. The infants and children were identified at the time of the intervention, and if the families consented, they were enrolled for follow-up visits six months after the intervention, at 18 months and at four to five years of age. A longer follow-up period would be optimal, but this has not been possible due to budget limitations. All surgical interventions were provided within the province of Alberta, but many children were referred from other western Canadian provinces (Saskatchewan, Manitoba and, to a lesser extent, British Columbia), so the follow-up was organized in their home province.

Table 1 summarizes current, discontinued and potential enrolment criteria. Some criteria were discontinued because literature reports or local experience analyzing and interpreting outcome data did not support ongoing follow-up (high-frequency oscillation), alternative follow-up activities were initiated (for children with specific types of tumours) or the risk status of specific groups was lower than originally

thought (cranial remodelling or fetal transfusions). The compliance rate for the children included in the registry was 99% at baseline, 100% at 18 months and 96% at four years.

Standardized, age-appropriate, multidisciplinary assessments have been used to evaluate all children enrolled in the follow-up program. The specific tests chosen were selected to provide comprehensive outcome assessments on the basis of published neonatal and cardiac follow-up reports, and of test characteristics, such as established reliability, validity and ease of administration. Contact was made at six to eight months postoperatively, and at 18 to 36 months, the Bayley Scales of Infant Development II (21) were administered (including the Mental Development Index, Psychomotor Development Index and Behavioural Scales); when it becomes available, the Bayley Scales of Infant Development III will be used, including the Adaptive Behaviour and Caregiver questionnaires. Ophthalmology reports were obtained, if possible, and audiological testing was repeated. At four years, the testing included a general health history and a physical examination; audiology and ophthalmology reports; Wechsler Preschool and Primary Scale of Intelligence – Third Edition (22); Test of Visual Motor Integration, Fifth Edition (23); and the Multiattribute Health Status Classification System (24).

The number of infants and children assessed to date is small for some of the intervention categories, so we have not summarized them separately. However, in general, cerebral palsy, and vision and hearing abnormalities have been infrequent in the study subjects. On the other hand, developmental delay has been found in 30% to 40% of the overall group, and cognitive skills have often been in the low-average range. Some of the details regarding other causes of morbidity in the group of infants with cardiac abnormalities were reported previously (3).

The program has been able to provide supportive advice when outcomes have been normal, to initiate interim intervention when mild to moderate health problems were identified and to make referrals for ongoing, more intensive intervention when disabilities were detected. Counselling of parents to ensure appropriate and realistic developmental and health expectations of their infants and children is provided during the assessment visits. Between 30% and 40% of the infants and children have been involved with early intervention programs.

By analyzing components of antenatal, neonatal, preoperative and operative measures, and postoperative care details in combination with outcome data, efforts have begun to improve the outcomes by influencing specific components of care. In addition, the outcome information collected has provided a basis for enhanced communication with parents and primary physicians about specific cardiac and other diagnoses in the children assessed. The program costs are comparable with costs in neonatal follow-up programs in general; while details regarding this are beyond the scope of the present article, it is noted that the longitudinal assessment costs are in the range of 3% to 4% of the costs related to the initial intervention and hospitalization.

TABLE 1
Enrolment criteria in a follow-up program for infants who received complex paediatric therapies

Enrolment criteria	n	Survivors
Current		
Fetal surgery	2	2
Complex cardiac surgery at six weeks or earlier (with or without ECMO)	269	236
Renal dialysis at 12 months or earlier	8	5
Liver, heart, lung or kidney transplants; ECMO; stem cell transplants; or postresuscitation cooling at five years or earlier	107	72
Paediatric ECMO (except that above) at five years or earlier	27	13
Discontinued		
Fetal transfusions	10	10
High-frequency oscillation	24	21
Specific tumours	30	28
Cranial remodelling	6	6
Potential		
Twin-to-twin transfusion	N/A	

ECMO Extracorporeal membrane oxygenation; N/A Not yet available

REFERENCES

1. Limperopolous C, Manjemer A, Shevell M, Rosenblatt B, Roblicek C, Tchervenkov C. Neurodevelopmental status of newborns and infants with congenital heart defects before and after surgery. J Pediatr 2000;137:638-45.
2. Hagemo P, Rasmussen M, Bryhn G, Vandvik I. Hypoplastic left heart syndrome: Multiprofessional follow-up in the mid-term following palliative procedures. Cardiol Young 1997;7:248-53.
3. Robertson CM, Joffe AR, Sauve RS, et al, with The Western Canadian Complex Pediatric Therapies Project Follow-Up Group. Outcomes from an interprovincial program of newborn open heart surgery. J Pediatr 2004;144:86-92.
4. Shillingford AJ, Wernovsky G. Academic performance and behavioral difficulties after neonatal and infant heart surgery. Pediatr Clin North Am 2004;51:1625-39, ix.
5. Tweddell JS, Spray TL. Newborn heart surgery: Reasonable expectations and outcomes. Pediatr Clin North Am 2004;51:1611-23, ix.
6. Nield TA, Langenbacher D, Poulsen MK, Platzker AC. Neurodevelopmental outcome at 3.5 years of age in children treated with extracorporeal life support: Relationship to primary diagnosis. J Pediatr 2000;136:338-44.
7. Ikle L, Ikle DN, Moreland SG, Fashaw LM, Waas N, Rosenberg AR. Survivors of neonatal extracorporeal membrane oxygenation at school age: Unusual findings on intelligence testing. Dev Med Child Neurol 1999;41:307-10.
8. Glass P, Wagner AE, Papero PH, et al. Neurodevelopmental status at age five years of neonates treated with extracorporeal membrane oxygenation. J Pediatr 1995;127:447-57.
9. The collaborative UK ECMO (Extracorporeal Membrane Oxygenation) trial: Follow-up to 1 year of age. Pediatrics 1998;101:E1.
10. Hobbs SA, Sexson SB. Cognitive development and learning in the pediatric organ transplant recipient. J Learn Disabil 1993;26:104-13.
11. Rasbury WC, Fennell RS III, Morris MK. Cognitive functioning of children with end-stage renal disease before and after successful transplantation. J Pediatr 1983;102:589-92.
12. Kennard BD, Stewart SM, Phelan-McAuliffe D, et al. Academic outcome in long-term survivors of pediatric liver transplantation. J Dev Behav Pediatr 1999;20:17-23.
13. Alonso EM, Neighbors K, Mattson C, et al. Functional outcomes of Pediatric Liver Transplantation. J Pediatr Gastroenterol Nutr 2003;37:155-60.

14. Adebäck P, Nemeth A, Fischler B. Cognitive and emotional outcome after pediatric liver transplantation. Pediatr Transpl 2003;7:385-9.
15. Hanvey L. Neonatal follow-up in Canada: Report of a survey, 1987. In: Feldman W, Paré C, eds. Neonatal Follow-up Programs in Canada. Proceedings of Ross Conference in Paediatrics. Montreal: Ross Laboratories, Division of Abbott Laboratories Ltd, 1987.
16. du Plessis AJ. Mechanisms of brain injury during infant cardiac surgery. Semin Pediatr Neurol 1999;6:32-47.
17. Ibrahim AE, Duncan BW, Blume ED, Jonas RA. Long-term follow-up of pediatric cardiac patients requiring mechanical circulatory support. Ann Thorac Surg 2000;69:186-92.
18. Cheung PY, Chui N, Joffe AR, Rebeyka IM, Roberson CM; Western Canadian Complex Pediatric Therapies Project, Follow-up Group. Postoperative lactate concentrations predict the outcome of infants aged 6 weeks or less after intracardiac surgery: A cohort follow-up to 18 months. J Thorac Cardiovasc Surg 2005;130:837-43.
19. Bellinger DC, Wypij D, du Plessis AL, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg 2003;126:1385-96.
20. McDonald SP, Craig JC; Australian and New Zealand Paediatric Nephrology Association. Long-term survival of children with end-stage renal disease. N Engl J Med 2004;350:2654-62.
21. Bayley N. Bayley Scales of Infant Development II. San Antonio: The Psychological Corporation, 1993.
22. Wechsler D. Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III). San Antonio: The Psychological Corporation, 2002.
23. Beery KE, Buktenica NA. Developmental Test of Visual Motor Integration, 5th edn. Minneapolis: NCS Pearson Inc, 2004.
24. Saigal S, Rosenbaum P, Stoskopf B, et al. Comprehensive assessment of the health status of extremely low birth weight children at eight years of age: Comparison with a reference group. J Pediatr 1994;125:411-7.