Original Article

Pediatric Heart Transplantation: Report from a Single Center in China

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Abstract

Background: Although heart transplantation (HTx) has become a standard therapy for end-stage heart diseases, experience with pediatric HTx is limited in China. In this article, we will try to provide the experience with indications, complications, perioperative management, immunosuppressive therapy, and survival for pediatric HTx based on our clinical work.

Methods: This is a retrospective chart review of the pediatric patients undergoing HTx at Department of Cardiovascular Surgery of Union Hospital from September 2008 to December 2014. We summarized the indications, surgical variables, postoperative complications, and survival for these patients.

Results: Nineteen pediatric patients presented for HTx at Union Hospital of Tongji Medical College, of whom 10 were male. The age at the time of transplantation ranged from 3 months to 18 years (median 15 years). Patient weight ranged from 5.2 kg to 57.0 kg (median 38.0 kg). Pretransplant diagnosis included cardiomyopathy (14 cases), complex congenital heart disease (3 cases), and tumor (2 cases). All recipients received ABO-compatible donor hearts. Postoperative complications occurred in 12 patients, including cardiac dysfunction, arrhythmia, pulmonary infection, renal dysfunction, and rejection. Two of them experienced cardiac failure and required extracorporeal membrane oxygenation. The immunosuppression regimen was comprised of prednisone, a calcineurin inhibitor, and mycophenolate. All patients recovered with New York Heart Association (NYHA) Class I–II cardiac function and were discharged. Only one patient suffered sudden death 19 months after transplantation.

Conclusion: Orthotopic HTx is a promising therapeutic option with satisfying survival for the pediatric population in China with end-stage heart disease.

Key words: China; Complications; Indications; Pediatric Heart Transplantation; Survival

Introduction

Pediatric heart transplantation (HTx) has become a successful treatment option for children with end-stage heart failure, with long-term survival attributed to advances in surgical techniques and immunosuppression regimens. Since Adrian Katrowitz performed the first pediatric HTx in 1967, more than 500 pediatric HTx are performed annually, mostly in Europe and North America.[1] However, experience with pediatric HTx from China is limited. In this study, we reported the 19 pediatric HTx at Union Hospital of Tongji Medical College, and try to explore the indications, complications, perioperative management, immunosuppressive therapy, and survival for pediatric HTx in China.

Methods

This study was approved by the Ethics Committee and performed in accordance with the ethical standards of the *Declaration of Helsinki*. All of the subjects recruited for the study provided written informed consent. Data were collected for HTx patients who were aged ≤18 years old at the time of transplantation from September 2008 to December 2014 at Union Hospital of Tongji Medical College. We summarized demographic data, pretransplant clinical history, surgical parameters, donor information,

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early postoperative management and complications, mortality, and immunosuppressive regimens for these recipients. Since endomyocardial biopsy was not performed at our institute, the diagnosis of rejection was based on clinical symptoms such as irritability, fatigue, heart failure, arrhythmias, electrocardiographic, and echocardiographic changes.

Descriptive data were presented as the mean ± standard deviation (SD) or median, as appropriate. Student's *t*-test was used to determine statistical significance. Logistic regression analysis was carried out to assess the impact of ischemic time on ventilation time, Intensive Care Unit (ICU) stay, and hospitalization time after operation. The SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A $P < 0.05$ was considered to be statistically significant.

Results

Patients' demographics

Nineteen pediatric patients underwent HTx at Union Hospital of Tongji Medical College, and one patient is still in the hospital now. The age at the time of transplantation ranged from 3 months to 18 years (mean 12.6 years old, median 15 years old). There were 10 male recipients. Patient weight ranged from 5.2 kg to 57.0 kg (mean 35.0 kg, median 38.0 kg). Pretransplant diagnosis included cardiomyopathy 14 cases (73.7%), complex congenital heart disease (CHD) 3 cases (15.8%), and tumor 2 cases (10.5%). The echocardiographic diagnosis for the first CHD recipient was viscera in versus, asplenia syndrome, totally anomalous pulmonary venous connection (supracardiac type), complete atrioventricular septal defect (Rastelli A type) with severe common atrioventricular valve regurgitation, single atrium, left ventricular dysplasia, double outlet of right ventricle, and pulmonary stenosis. The diagnosis for the second was dextrocardia, complete atrioventricular septal defect (Rastelli C type) with severe common atrioventricular valve regurgitation, single atrium, single ventricle, pulmonary stenosis and dextro aortic arch. The third was right ventricular hypoplasia syndrome, patent ductus arteriosus, tricuspid valve dysplasia with ebstein anomaly, pulmonary atresia with intact ventricular septum (PA-IVS) associated with right-ventricular dependent coronary circulation (RVDCC). Postoperative pathological diagnosis of the two patients with tumor were infiltrating lipoma involving left and right ventricle and low-grade myofibroblastic sarcoma in left atrium, respectively. Two patients had cardiac surgery, and one had exploratory thoracotomy surgery prior to HTx. All the patients had New York Heart Association (NYHA) Class IV heart failure prior to transplant. All the patients had panel reactive antibody (PRA) <10%, and received ABO-compatible donor hearts. Donor/recipient (D/R) weight ratio ranged from 0.7 to 2.7 (mean 1.6, median 1.5) [Table 1].

Surgical parameters

The total donor graft ischemic time ranged from 106 min to 490 min (mean 267.9 min, median 150 min). The cardiopulmonary bypass (CPB) time ranged from 71 min to 217 min (mean 123.4 min, median 112 min). Seventeen patients underwent biatrial anastomosis; two patients underwent bicaval anastomosis for anomalous pulmonary venous connection and dextrocardia. Three patients left the operating room with delayed chest closure, and two of these

Table 1: Characteristics of the 19 patients undergoing HTx

Number	Gender	Age (years)	Weight (kg)	Operation date	Pretransplant diagnosis	Mean PAP (mmHg)	EF (%)	D/R blood type	D/R weight ratio
1	Male	18	45.5	5/9/2008	DCM	44	20	AB–AB	1.5
2	Male	18	45.0	28/11/2008	DCM	20	28	O–O	1.1
3	Male	16	56.0	11/6/2009	DCM	–	31	O–AB	1.2
4	Male	16	51.0	10/7/2009	DCM	–	18	O–O	1.1
5	Male	13	45.0	20/11/2009	DCM	22	19	A–A	1.4
6	Female	15	40.0	28/11/2010	RCM	35	–	O–O	1.8
7	Male	16	57.0	14/12/2011	DCM	48	38	A–A	1.2
8	Female	16	38.0	7/9/2012	Tumor	–	72	O–O	1.6
9	Male	18	50.0	15/8/2013	CHD	32	19	B–B	1.4
10	Male	11	28.0	7/3/2014	DCM	26	16	B–AB	2.7
11	Female	11	26.0	30/3/2014	CHD	30	–	B–B	2.5
12	Female	14	36.0	16/5/2014	HCM	46	38	O–O	1.8
13	Female	18	29.0	6/8/2014	DCM	27	29	A–A	1.7
14	Female	8	21.0	21/9/2014	HCM	–	56	A–A	0.7
15	Male	10 months	7.5	23/9/2014	DCM	–	15	O–O	1.7
16	Female	6	18.0	28/9/2014	DCM	–	26	O–O	0.7
17	Female	17	49.0	21/10/2014	LA tumor	52	51	B–B	1.2
18	Female	8	18.0	20/11/2014	DCM	25	64	O–O	2.3
19	Male	3 months	5.2	22/11/2014	CHD	–	70	B–B	2.7

HTx: Heart transplantation; D: Donor; R: Recipient; PAP: Pulmonary arterial pressure; EF: Ejection fraction; DCM: Dilated cardiomyopathy; RCM: Restrictive cardiomyopathy; HCM: Hypertrophic cardiomyopathy; CHD: Congenital heart disease; LA: Left atrial.

three patients experienced cardiac failure following HTx requiring extracorporeal membrane oxygenation (ECMO). In both patients, cannulation was achieved via a transthoracic approach in the operation room. A centrifugal pump was utilized due to smaller size and the ease of deployment. ECMO was withdrawn 74 h and 115 h later, respectively. The third patient required delayed closure because the pericardial cavity was not enough for a large donor heart [Table 2].

Table 2: Surgical characteristics of 19 patients

Number	Ischemic time (min)	Surgical type	CPB time (min)	Delayed chest closure	Mechanical circulatory support
1	106	Biatrial	138	No	No
2	120	Biatrial	86	No	No
3	133	Biatrial	96	No	No
4	119	Biatrial	97	No	No
5	127	Biatrial	104	No	No
6	154	Biatrial	113	No	No
7	150	Biatrial	112	No	No
8	442	Biatrial	117	No	No
9	388	Bicaval	201	No	No
10	121	Biatrial	71	No	No
11	248	Bicaval	174	No	No
12	139	Biatrial	86	No	No
13	490	Biatrial	114	No	No
14	452	Biatrial	217	Yes	ECMO 74 h
15	379	Biatrial	97	Yes	ECMO 115 h
16	130	Biatrial	90	No	No
17	482	Biatrial	179	No	No
18	522	Biatrial	107	No	No
19	388	Biatrial	146	Yes	No

CPB: Cardiopulmonary bypass; ECMO: Extracorporeal membrane oxygenation.

Postoperative management

Postoperative time to first extubation ranged from 15 h to 348 h (median 24 h). ICU stay ranged from 3 days to 35 days (mean 13.5 days, median 7 days). Since isolation ward were not available until 2010, ICU stay was longer. Inotropic support after operation ranged from 1 day to 12 days (mean 5.2 days, median 5 days). Postoperative complications occurred in 12 patients, including cardiac dysfunction (4 cases), arrhythmia (3 cases), pulmonary infection (6 cases), renal dysfunction (2 cases), and rejection (3 cases). Among the four patients with heart failure, two required ECMO in the operation room due to difficulty in weaning off CPB. The other two suffered heart failure after surgery, with clinical manifestations of low blood pressure, high central venous pressure, tachycardia, clammy extremities, edema, and decreased exercise tolerance. For these two patients, inotropic agents, nesiritide, diuretics, beta blockers, and vasodilators were used in combination. Frequent atrial fibrillation and ventricular premature beats were the most common type of arrhythmias observed in the recipients. After excluding cardiac structure abnormality by echocardiography, we increased the dose of anti-rejection drugs and amiodarone as symptomatic therapy. Then the rhythm converted to sinus rhythm. Two patients required peritoneal dialysis in the immediate postoperative period and both experienced a full recovery of renal function. All patients achieved a postoperative EF value of at least 50% and had NYHA Class I–II cardiac function prior to discharge. All the patients returned for follow-up care, and the length of follow-up ranged from 1 month to 70 months. One patient suffered sudden death, 19 months later after discharge. The patient probably died of primary graft failure [Table 3].

Table 3: Postoperative characteristics and survival of 19 patients

Number	Ventilation time (h)	ICU stay (days)	Inotropic support time (days)	Complications	EF 3 weeks after operation (%)	Hospitalization time after operation (days)	Survival status
1	25	33	6	HF, pneumonia, rejection	67	42	Deceased
2	18	35	3	Pneumonia	65	46	Alive
3	18	31	6	Arrhythmia	62	50	Alive
4	20	29	4	No	67	34	Alive
5	42	25	6	Arrhythmia, rejection	70	37	Alive
6	24	7	6	Pneumonia	63	34	Alive
7	28	4	5	rejection	74	27	Alive
8	24	5	5	No	70	20	Alive
9	22	7	6	Arrhythmia	74	58	Alive
10	19	7	1	No	78	26	Alive
11	19	9	1	HF	59	43	Alive
12	16	7	6	No	66	25	Alive
13	36	3	3	No	77	21	Alive
14	348	9	12	HF	59	29	Alive
15	312	21	5	HF, pneumonia, renal dysfunction	62	84	Alive
16	15	3	4	No	62	23	Alive
17	35	7	8	No	70	27	Alive
18	112	6	3	Pneumonia	65	36	Alive
19	164	9	9	Pneumonia, renal dysfunction	–	–	Hospital stay

ICU: Intensive care unit; HF: Heart failure; EF: Ejection fraction.

Immunosuppression protocol

Interleukin-2 receptor antagonist (IL-2RA, basiliximab) was used for induction therapy in all recipients. The first dose (20 mg for children <35 kg, 40 mg for children ≥35 kg) was administered intravenously 2 h prior to the operation. The second dose was administered intravenously 4 days after transplantation. Maintenance immunotherapy consisted of cyclosporine, mycophenolate, and prednisone before 2011, while triple therapy of tacrolimus, mycophenolate, and prednisone were used from 2011 onward. One of the advantages of new regimens was reduced occurrence of side-effects such as nephrotoxicity, hepatotoxicity, hirsutism, gingival hyperplasia, nausea, and diarrhea.

Overview of heart transplantation at our institution

A total of 203 cases of HTx were performed at our center since September 2008, and 84 of those cases were performed in 2014. The proportion of pediatric HTx in 2014 has increased compared to the past (11.9% vs. 7.6%). Moreover, pediatric HTx were performed at a younger age (9.40 ± 6.06 years vs. 16.20 ± 1.64 years, $t = 3.258$, $P = 0.005$) and a lower weight (23.77 ± 12.99 kg vs. 47.50 ± 6.55 kg, $t = 4.932$, $P < 0.001$) [Figure 1]. Another breakthrough was the successful HTx in two infants. One of these infants was 3 months old, perhaps the youngest heart transplant recipient in China's history. The baby was diagnosed with PA-IVS associated with RVDCC.

Discussion

Pediatric HTx has continued to evolve since a case reported in 1967.[2] With advances in surgical strategies and medical therapies, the outcomes have greatly improved. However, pediatric HTx in China is still in its infancy, and there is still much to explore. The present article retrospectively analyzed surgical indications, perioperative management, complications, and short-term survival at our center.

Dilated cardiomyopathy is the most common indication for pediatric HTx at our center, which was consistent with the data from the registry of the International Society for Heart and Lung Transplantation (ISHLT).[1,3] The incidence of dilated cardiomyopathy is 0.58 per 100,000 children and accounts for over 50% of cardiomyopathy in the USA.[4] However, pediatric DCM in China lacks large-scale epidemiological survey. Patients with DCM have relatively low waitlist mortality.[5] Towbin *et al*.[6] reported that freedom from death or transplantation at 1 and 5 years after DCM diagnosis was 69% and 54%, respectively. DCM patients submitted to HTx underwent the surgery at our center at relatively older age, except for one infant. The surgical correction and palliation in children with CHD has improved significantly. Moreover, 3-month posttransplant survival for children with a diagnosis of CHD has been reported worse than children with cardiomyopathy.[7] Single-center studies also demonstrated an increase in perioperative mortality associated with neonatal age and pulmonary reconstruction.[8] Therefore, primary transplant for CHD in which palliative operation is feasible is not recommended. Recently, we presented a 3-month-old infant with HTx, diagnosed PA-IVS associated with RVDCC, without an obvious symptom of cyanosis, but frequent episodes of heart failure. Palliation surgery may not be a good choice for him. A recent study also suggested early consideration of transplantation in PA-IVS patients with RVDCC.[9]

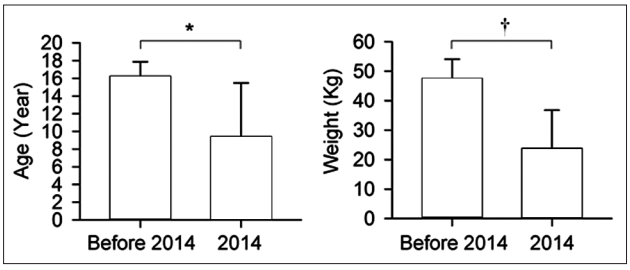

Figure 1: Trend of pediatric heart transplantation at our institute. Pediatric heart transplantation in 2014 were performed at a younger age ($t = 3.258$, $^*P = 0.005$) and a lower weight ($t = 4.932$, $^\dagger P < 0.001$) than those in the past.

The overall survival after HTx for the pediatric population is approximately 90% at 1 year.[1] The survival rate during hospitalization is 100% at our center. All patients were followed after discharge. The follow-up time ranged from 1 month to 70 months. Only one patient suddenly died of primary graft failure, which accounted for more than half of death within the first 3 years after transplantation in the presence of rejection.[1] Donor characteristics have been shown to affect pediatric HTx. While donor cause of death, inotropic agents use, and cardiopulmonary resuscitation were demonstrated less impact on outcomes than previously thought, longer ischemic time is still an important risk factor that can affect 1-year survival.[10] Furthermore, the longer ischemic time has been associated with a longer period of ventilator dependence and longer stay in the ICU.[11] However, the present study did not find an association among the above parameters, probably due to smaller patient numbers (data not shown).

Early postoperative management after pediatric HTx is crucial to success. Postoperative complications were closely associated with mortality during hospitalization and long-term survival. Cardiac dysfunction and pulmonary infection are the most common complications at our center. Infection accounts for approximately 12% of deaths during the 1st year after transplantation.[1] Pathogens are typically bacterial, virus, and relatively uncommon fungus. One single-center study demonstrated that infants were more likely to experience more severe and chronic infection.[12] Immunosuppression renders the receipts susceptible to infection, particularly with opportunistic agents. We need to find the balance between anti-rejection and anti-infection therapies. The ISHLT data have identified renal dysfunction as an important risk factor for 1-year pediatric heart transplant survival. Previous studies demonstrated the adverse effects of renal failure on perioperative graft loss.[13] There were no occurrences of graft vascular disease or lymphoproliferative disease during the follow-up.

Postoperative rejection-induced hemodynamic compromise can affect long-term survival.[14] The endomyocardial biopsy is the gold standard for routine surveillance of cardiac allograft rejection. However, the diagnosis of rejection at our institute was performed mainly by clinical symptoms such as irritability, fatigue, heart failure, arrhythmias, electrocardiographic, and echocardiographic changes. Our immunosuppression protocol consisted of a calcineurin inhibitor and cytostatic. We originally used cyclosporine, but it has been replaced by tacrolimus due to its improved side-effect profile.

ECMO is the most feasible form of mechanical circulatory support and a practical option for pediatric HTx patients who are unable to wean from CPB or with the inadequate postoperative cardiac output.[15,16] Vanderlaan *et al*.[13] reported that both pre- and post-transplant use of ECMO was associated with an increased risk of perioperative graft loss. Two patients experienced cardiac failure following HTx requiring ECMO at our center. Both were cannulated via a transthoracic approach in the operation room after they could not be weaned from CPB. The ECMO support time was 74 h and 115 h, respectively. They both survived to hospital discharge. We regarded the posttransplant use of ECMO as a useful strategy for patients with graft dysfunction, allowing time for cardiac rest and gradual adaptation to a new hemodynamic environment. Another single-center retrospective study demonstrated that ECMO could provide effective hemodynamic support, improving postoperative survival as well.[17] However, the sample size was small. We speculated that ECMO complications and precannualation end-organ condition may make it difficult to determine the positive effect of ECMO on survival. A larger multicenter study would be required to explore the effect of ECMO on postoperative survival.

Eighty-four HTx were implemented in our center in 2014, ranking first in China. The proportion of pediatric recipients <1-year old has increased gradually. Our study showed that short-term results of pediatric HTx at our institution were quite satisfactory and complication rates were acceptable. Relative to adults, pediatric heart transplant recipients still face greater organ shortages, and transplant operations can be more difficult due to technical difficulties imposed by some congenital malformations. Despite these disadvantages, pediatric HTx is a feasible and promising procedure in China. However, large registries and long-term survival remain to be assessed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Dipchand AI, Kirk R, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, *et al.* The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Pediatric Heart Transplantation Report-2013; focus theme: Age. J Heart Lung Transplant 2013;32:979-88.
2. Kantrowitz A, Haller JD, Joos H, Cerruti MM, Carstensen HE. Transplantation of the heart in an infant and an adult. Am J Cardiol 1968;22:782-90.
3. Voeller RK, Epstein DJ, Guthrie TJ, Gandhi SK, Canter CE, Huddleston CB. Trends in the indications and survival in pediatric heart transplants: A 24-year single-center experience in 307 patients. Ann Thorac Surg 2012;94:807-15.
4. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, *et al.* The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003;348:1647-55.
5. Kirk R, Naftel D, Hoffman TM, Almond C, Boyle G, Caldwell RL, *et al.* Outcome of pediatric patients with dilated cardiomyopathy listed for transplant: A multi-institutional study. J Heart Lung Transplant 2009;28:1322-8.
6. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, *et al.* Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 2006;296:1867-76.
7. Lamour JM, Kanter KR, Naftel DC, Chrisant MR, Morrow WR, Clemson BS, *et al.* The effect of age, diagnosis, and previous surgery in children and adults undergoing heart transplantation for congenital heart disease. J Am Coll Cardiol 2009;54:160-5.
8. Chen JM, Davies RR, Mital SR, Mercando ML, Addonizio LJ, Pinney SP, *et al.* Trends and outcomes in transplantation for complex congenital heart disease: 1984 to 2004. Ann Thorac Surg 2004;78:1352-61.
9. Cheung EW, Richmond ME, Turner ME, Bacha EA, Torres AJ. Pulmonary atresia/intact ventricular septum: Influence of coronary anatomy on single-ventricle outcome. Ann Thorac Surg 2014;98:1371-7.
10. Conway J, Chin C, Kemna M, Burch M, Barnes A, Tresler M, *et al.* Donors' characteristics and impact on outcomes in pediatric heart transplant recipients. Pediatr Transplant 2013;17:774-81.
11. Rodrigues W, Carr M, Ridout D, Carter K, Hulme SL, Simmonds J, *et al.* Total donor ischemic time: Relationship to early hemodynamics and intensive care morbidity in pediatric cardiac transplant recipients. Pediatr Crit Care Med 2011;12:660-6.
12. Kulikowska A, Boslaugh SE, Huddleston CB, Gandhi SK, Gumbiner C, Canter CE. Infectious, malignant, and autoimmune complications in pediatric heart transplant recipients. J Pediatr 2008;152:671-7.
13. Vanderlaan RD, Manlhiot C, Conway J, Honjo O, McCrindle BW, Dipchand AI. Perioperative factors associated with in-hospital mortality or retransplantation in pediatric heart transplant recipients. J Thorac Cardiovasc Surg 2014;148:282-9.
14. Gossett JG, Canter CE, Zheng J, Schechtman K, Blume ED, Rodgers S, *et al.* Decline in rejection in the first year after pediatric cardiac transplantation: A multi-institutional study. J Heart Lung Transplant 2010;29:625-32.
15. Kane DA, Thiagarajan RR, Wypij D, Scheurer MA, Fynn-Thompson F, Emani S, *et al.* Rapid-response extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in children with cardiac disease. Circulation 2010;122 11 Suppl: S241-8.
16. Kelly RB, Harrison RE. Outcome predictors of pediatric extracorporeal cardiopulmonary resuscitation. Pediatr Cardiol 2010;31:626-33.
17. Su JA, Kelly RB, Grogan T, Elashoff D, Alejos JC. Extracorporeal membrane oxygenation support after pediatric orthotopic heart transplantation. Pediatr Transplant 2015;19:68-75.