

Early experience with pediatric cardiac transplantation in a limited resource setting

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ABSTRACT

- Background** : Pediatric heart transplantation is now a well-established and standard treatment option for end stage heart failure for various conditions in children. Due to logistic issues, it is not an option for in most pediatric cardiac centres in the third world.
- Aim** : We sought to describe our early experience in the current era in India.
- Methods** : This is a short term retrospective chart review of pediatric patients who underwent heart transplantation at our centre. Mean/Median with standard deviation /range was used to present data.
- Results** : Twenty patients underwent orthotopic heart transplant between January 2016 and June 2019. The median age at transplant was 12.4years (range 3.3 to 17.3 years). The median weight was 23.2kg (range 10-80kg). The mean donor/recipient weight ratio was 1.62± 0.84. The mean ICU stay was 12.1days. The mean follow up post transplant was 2.03± 0.97years (range 10 days-3.57years). The 1 month and the 1 year survival was 100%. Biopsies were positive for significant rejection in 7 patients (35%). At the time of last follow-up, 3 patients (15%) had expired. The major post transplant morbidities were mechanical circulatory support (*n*=3), hypertension with seizure complex (*n*=3), post transplant lympho-proliferative disorder (*n*=1), pseudocyst of pancreas (*n*=1), coronary allograft vasculopathy (*n*=3) and systemic hypertension (*n*=7). All surviving patients (*n*=17) were asymptomatic at last follow up.
- Conclusion** : The results suggest acceptable short term outcomes in Indian pediatric patients can be achieved after heart transplantation in the current era. Significant rejection episodes and coronary allograft vasculopathy need careful follow up.
- Keywords** : Dilated cardiomyopathy, endomyocardial biopsy, heart failure, heart transplant, mechanical circulatory support, pediatrics, restrictive cardiomyopathy

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INTRODUCTION

Cardiac transplant is a well-established option for patients with end-stage heart disease.^[1,2] Although the first cardiac transplant in India took place barely months after the world's first in 1967^[3] (the world's first pediatric heart transplant took place 3 days after the adult), it never took up its rightful place as a viable therapeutic option till recent times. A handful of centers across India now offer this modality.^[4-7] We sought to describe our early experience with pediatric heart transplantation and follow-up in the current era.

METHODS

Waiver of informed consent was granted from the hospital's ethics committee. Records of pediatric patients who underwent heart transplant from January 2016 to June 2019 were analyzed. Data have been tabulated and expressed as frequency, mean with standard deviation (SD), and median with range as applicable.

RESULTS

Demographics

Twenty pediatric patients underwent heart transplant during the study period [Table 1]. The median age at transplant was 12.4 years (range: 3.3–17.3 years). The median weight was 23.2 kg (range: 10–80 kg). There were thirty patients listed during the study period, of which five expired while listed, three were delisted, and two remained on the list, thereby leaving twenty patients who are the subjects of this study. The median wait-listed time was 3.4 months (range: 1 week–18 months) [Figure 1].

Pretransplant workup

Echocardiography

Dilated cardiomyopathy (DCM) patients ($n = 15$): The mean z score of the left ventricular (LV) end-diastolic dimension was + 3.7 (SD: 1.2) and LV end-systolic dimension was + 4.23 (SD: 1). The mean LV ejection fraction was $17.3\% \pm 7\%$ at the time of transplant.

Table 1: Demographic profile of recipients

Case number	Age at transplant (years)/sex	Weight (kg) at transplant	Diagnosis	Last follow-up (June 2019)	Ventricular function at last follow-up
1	17.3/female	43.1	DCM	Alive	Normal
2	7.8/female	27.7	DCM	Alive	Normal
3	16.6/male	38	DCM	Expired	
4	15.6/female	43.5	RCM	Alive	Normal
5	14.6/male	23	DCM	Expired	
6	17.3/male	29	RCM	Expired	
7	10.3/male	20	DCM	Alive	Normal
8	16.3/male	80	DCM	Alive	Normal
9	15.2/male	50	DCM	Alive	Normal
10	11.1/male	21.2	RCM	Alive	Normal
11	13.8/female	28.7	DCM	Alive	Normal
12	4.5/female	13	DCM	Alive	Normal
13	8.1/male	19	Uhl's anomaly	Alive	Normal
14	10.8/female	20.3	DCM	Alive	Normal
15	3.3/male	15	DCM	Alive	Normal
16	14.6/male	25.6	DCM	Alive	Normal
17	16.4/male	47.3	DCM	Alive	Normal
18	8.3/female	15.4	DCM	Alive	Normal
19	4.5/female	10	DCM	Alive	Normal
20	9.9/female	20	s/p Glenn	Alive	Normal

DCM: Dilated cardiomyopathy, RCM: Restricted cardiomyopathy

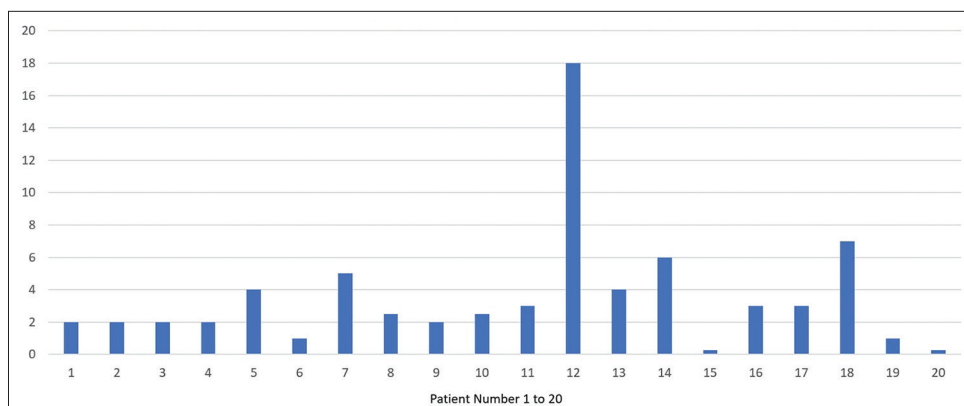


Figure 1: The time spent on the wait list for each patient (in months)

Six of the 15 patients had noncompaction of the LV. Restricted cardiomyopathy patients (n = 3): There was severe diastolic dysfunction associated with thrombi in the right atrium (n = 2) and pericardial and pleural effusions (n = 3). The biventricular systolic function was normal in two of the three patients. There was mild LV systolic dysfunction in one. Only one patient had pulmonary hypertension (mild). Congenital heart disease (n = 2): One patient had Uhl’s anomaly with severe right ventricular (RV) dysfunction. The second patient, aged 9.9 years, had a bidirectional Glenn shunt for a functional single-ventricle anatomy in infancy. She was lost to follow-up before presenting to us with worsening hyperviscosity syndrome and severe systolic and diastolic ventricular dysfunction.

Cardiac catheterization

Table 2 shows that cardiac catheterization was performed at the discretion of the clinical team. Pulmonary vasodilator testing with oxygen and intravenous sildenafil (0.4 mg/kg over 10 min) was performed if the transpulmonary gradient was elevated (>12 mmHg).

Other pretransplant workup

Human leukocyte antigen (HLA) panel reactive immunoglobulin (Ig) G antibodies (PRA) for HLA Class 2 antibodies was positive (30%, Class II) in 1 patient out of 17 tested. Donor cytomegalovirus (CMV) IgG antibody titers were protective in 14 of 19 patients whose reports were available and Epstein-Barr virus (EBV) IgG antibody titers were protective in 6 of 17 available records.

Details of the cardiac transplantation procedures

Donor-recipient data

The most common cause of death in the donor was traumatic head injury. The donor heart was mobilized from within the city in seven of twenty patients. The mean donor age was 19 ± 12.9 years and weight was 38.5 ± 14.9 kg. The mean donor-to-recipient weight ratio was 1.62 ± 0.84 [Figure 2]. Four of the twenty donors had moderate LV dysfunction on their preretrieval echocardiograms which responded to titration of inotropes. One donor heart had mild aortic regurgitation. Donor-specific antibody (DSA) testing was obtained in the last ten transplants; all were negative except one.

Cardiac transplant surgery

Orthotopic heart transplant was performed by standard bicaval anastomotic technique. After ensuring optimal size and function and no significant valvular lesions, the donor heart was harvested after infusing a single 30 ml/kg dose of custodiol solution. Another dose was repeated if the ischemic time crossed 180 min. The mean cold ischemic time was 178.6 ± 49.7 min (range: 90 min–245 min) [Figure 3]. Immunosuppression induction was with intravenous basiliximab (20 mg or 10 mg for recipient weight <30 kg) and methylprednisolone (30 mg/kg).

Intensive care unit and hospital course

All patients were received on adrenaline (0.5 mcg/kg/min) and milrinone (0.3 mcg/kg/min) drips and also on

Table 2: Cardiac catheterization data

Patient number	Diagnosis	Mean PA pressure (mmHg)	LVEDP (mmHg)	TPG pre/postsildenafil + oxygen	PVRi (WU) pre/postsildenafil + oxygen	CI (L/min/m ²)
5	DCM	39	17	19/5	5.59/2.14	3.6
6	DCM	42	25	17/6	4.53/1.54	3.2
16	DCM	34	11	23/17	6.6/4.77	3.28
18	RCM	21	13	5/-	2.43/-	2
20	s/p Glenn	18	15	3/-	1/-	

DCM: Dilated cardiomyopathy, RCM: Restricted cardiomyopathy, CI: Cardiac index, LVEDP: LV end-diastolic pressure, TPG: Transpulmonary gradient, PVRi: Pulmonary vascular resistance indexed

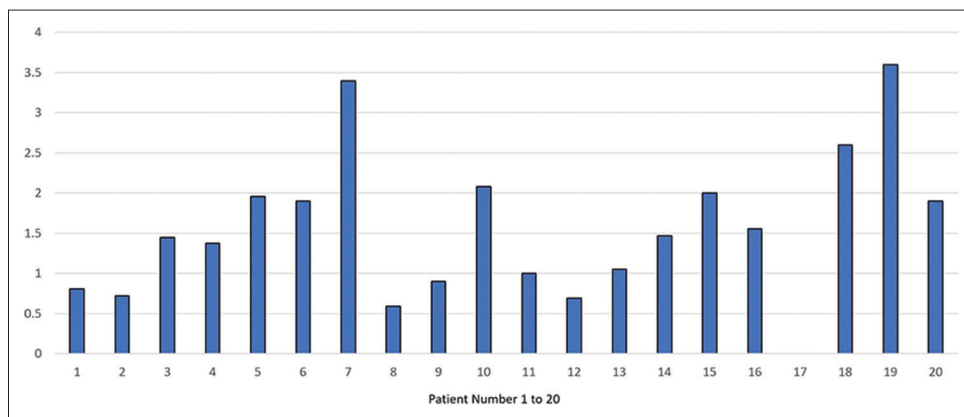


Figure 2: The donor-to-recipient weight ratio for each patient. Donor weight was not available for patient #17

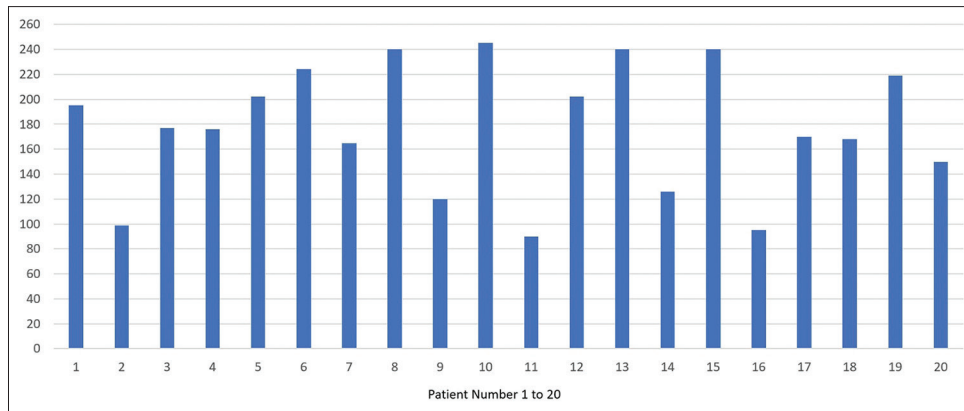


Figure 3: Ischemic time (in minutes) for each patient

fentanyl infusions. Noradrenaline and/or inhaled nitric oxide/sildenafil (0.67/mg/kg/h) was added if required. Pressure control mode ventilation was used. Three patients were placed on mechanical circulatory support (MCS) after coming off bypass (details in section 9.2). The mean intensive care unit (ICU) stay was for 12.1 ± 5.4 days (range: 7–27 days). The mean stay in the ward was 10 ± 5.4 days. The pre-discharge echocardiogram showed normal biventricular systolic function in all patients except one with mild LV dysfunction.

Induction, maintenance immunosuppression, and other medications

Protocol followed was methylprednisolone and basiliximab intraoperatively and tacrolimus, mycophenolate mofetil (MMF), and prednisolone for postoperative maintenance immunosuppression.^[8] Tacrolimus was initiated at 0.5 mg bd (on day 4 posttransplant) and then titrated. MMF was dosed at 20 mg/kg/dose twice daily starting on postoperative day (POD) 1. Prednisolone was given at 2.5–5 mg per day for the first 12 months posttransplant. Valganciclovir, trimethoprim-sulfamethoxazole, and a statin were added to drug regimen by days 4–5.

Postdischarge course

Outpatient course

The mean follow-up period posttransplant was 2.03 ± 0.97 years (range: 0.02–3.57 years). The scheduled follow-up plan was once every 2 weeks for the first 3 months, then once a month for the next 3 months, and then every 3 months till 1 year posttransplant. Subsequently, follow-up was once every 6 months or sooner as dictated by individual patient needs. Echocardiograms documented normal biventricular function in all surviving patients at the last follow-up. EBV polymerase chain reactions were performed periodically in patients with low titers of EBV antibodies pretransplant. Complete blood count and serum creatinine were obtained 3–6 monthly. We had no instance of elevated creatinine levels in our

pediatric patient population. Occasional gastrointestinal disturbances or leukopenia were noted that responded to suspending mycophenolate temporarily. Target serum tacrolimus trough levels posttransplant were 10–12 ng/ml (first 6 months), 8–10 ng/ml (6–12 months), and 7–8 ng/ml beyond 12 months from transplant. The dose was uptitrated in the presence of rejection. Mycophenolate was replaced by everolimus/sirolimus in the presence of coronary allograft vasculopathy (CAV). All surviving patients reported a good quality of life with resumption of all routine activities.

Biopsies and coronary angiograms

Surveillance endomyocardial biopsy was performed at 1 month and then annually posttransplant. Jugular or femoral (for <25 kg weight) approach was used. Rejection in the biopsies was classified according to the International Society for Heart and Lung Transplantation (ISHLT) consensus statement revised in 2005.^[9] Coronary angiograms were routinely performed on all patients on an annual basis.

Mortality

The 30-day and 1-year mortality was 0. Three patients expired between 1 and 2 years posttransplant. Two adolescent boys had confirmed noncompliance with their immunosuppressants. One of them [patient #3, Table 1] expired from heart failure due to antibody-mediated rejection (AMR) Grade 2, confirmed on biopsy, while the other [patient #6, Table 1] expired before reaching a hospital. The third patient [patient #5, Table 1] expired after failed treatment for acute AMR Grade 2 despite compliance. Till the end of the study period (June 2019), the remaining 17 patients are alive and well.

Morbidity

Graft rejection

A significant grade of rejection (> cell-mediated rejection (CMR) 2R or any grade of AMR) was documented through biopsy in 7 patients out of 20 (35%) [Figure 4]. Two of the seven had AMR Grade 2 and were symptomatic

and both expired. All the others had AMR Grade 1. The tacrolimus dose was adjusted to achieve a higher serum trough level in such patients as none had clinical or echocardiographic evidence of rejection. None of the AMR-positive biopsy patients had DSA testing performed as the transplants were dated before DSA tests were made essential in our protocol. PRA status was negative in all biopsy-positive patients.

Mechanical circulatory support

Preoperatively, one patient (patient #17) required extracorporeal membrane oxygenation (ECMO) for shock and reduced RV contractility. Postoperatively, three patients required MCS. One patient (patient #10) had mild biventricular dysfunction and severe pulmonary hypertension after coming off pump, and he was placed on ECMO. He could be decannulated 5 days later. The second patient (patient #13) received a heart from a donor who had arrested during harvesting. Severe LV dysfunction was noted postcardiopulmonary bypass (CPB), and he was placed on ECMO for 48 h. The third patient (patient #19) was a critically ill child with DCM who was placed on left ventricular assist device for severe LV dysfunction postoperatively. The left atrium was cannulated for inflow, and the aortic cannula used for CPB was continued for outflow. This child also had an oversized donor (weight ratio: 3.6). As the myocardial edema resolved, the patient was able to be decannulated on POD 5.

Big heart syndrome

This was observed in three patients. The donor-to-recipient weight ratio range was 2–3.6 in these patients. These patients had persistent systemic hypertension and also 1–2 episodes of seizures.

Hypertension

The most common side effect was hypertension; it was seen in seven patients, in one of whom, it was pretransplant. It was associated with seizures (see above) in three patients. It was presumed to be related to the neurohormonal derangement or drug side effect in three patients. The hypertension was controlled by enalapril and/or amlodipine.^[10]

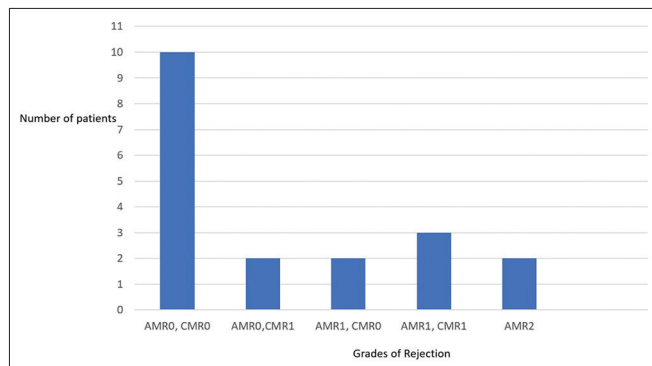


Figure 4: Grades of rejection encountered in patients. The highest grade of rejection seen in every patient has been recorded

Posttransplant lymphoproliferative disorder

This was seen in one patient (case #10), 1 year posttransplant. He presented with tonsillar abscesses, which was a manifestation of B-cell myeloproliferative disorder (diffuse large B-cell lymphoma). The patient’s preoperative EBV antibody titers were low (nonprotective). He was aggressively treated with eight cycles of IV rituximab successfully and is currently clinically stable on a modified immunosuppression regimen with normal cardiac allograft function and negative endomyocardial biopsy.

Coronary allograft vasculopathy

Four patients were diagnosed with CAV (all were Grade 1, ISHLT classification) on the basis of their annual coronary angiograms. Three of the four patients had no prior significant grade of rejection on biopsy, and none had CMV infection posttransplant. One of the four patients likely had preexisting (donor) related disease.

Pancreatic pseudocyst

This was seen in one patient [patient #12, Table 1], 9 months posttransplant who presented with depressed appetite, vomiting, and abdominal distension. She underwent successful endoscopic pseudocyst fluid drainage.

Infections

Four patients (20%) had a positive bacterial blood culture in the ICU posttransplant, which were successfully treated with intravenous antibiotics. One [#10, Table 1] of the four patients had a sternal infection as well. None of the donor blood cultures were positive. Urinary tract infection (*Escherichia coli* in the urine) was seen in one patient (patient #12) who presented with fever within the first 3 months posttransplant. There were no other proven bacterial, CMV, or fungal infections seen till the end of the study period.

Other morbidities

Elevated lipid levels were seen in three patients posttransplant, one of whom had preexisting hypothyroidism, obesity, and hyperlipidemia. All three patients are on statins and also appropriate diet. Mild hyperglycemia was observed in two patients [patient #12 and 14, Table 1].^[11]

DISCUSSION

Pediatric heart transplantation is the standard of care for the management of decompensated heart failure.^[1,2] The ISHLT offers comprehensive guidelines on care of patients.^[12] Few publications sharing their experience and outcome data are from outside the Western world.^[13]

Rejection

Recent pediatric heart transplant studies and data from ISHLT database suggest an early (treated) rejection

incidence of 15%–22% in the 1st year posttransplant that is improving as management protocols improve over eras.^[1,14] Our case series had two patients with treated rejection between 1 and 2 years of transplant. Paucity of local HLA laboratories, longer wait times to run HLA profiles, as well as financial constraints meant that HLA typing of donors (and prospective crossmatch) were not routinely performed at our center initially. However, our protocol now includes HLA typing of all donors. Flow-based single antigen bead (SAB) testing is performed on prospective recipients with positive (>10%) PRAs to detect HLA-specific antibodies.^[15,16] With these changes, we are able to perform a virtual crossmatch utilizing the donor HLA profiles and the SAB results of the prospective recipients. Noncompliance in the adolescent population is not unexpected. We believe that there were elements of local nonavailability/delayed availability of the immunosuppressants as also cost factors that contributed to risk-taking behavior. The two deaths in our series seem avoidable. We have, since then, made our pretransplant psychosocial counseling and screening process even more stringent.

Big heart syndrome

This refers to the clinical scenario of a hypertension and seizures seen in a situation of an oversized donor allograft used to pumping into a large body, suddenly encountering “reduced” afterload in the recipient body.^[17] Anticipation of this phenomenon in a patient with a high donor/recipient weight ratio will prevent unnecessary workup of seizures and hypertension.

Posttransplant lymphoproliferative disorder

In the pediatric postheart transplant population, posttransplant lymphoproliferative disorder (PTLD) has an incidence of 9%, 15%, and 28% at 3, 5, and 10 years, respectively.^[18] EBV is involved in its etiopathogenesis, and EBV-negative (susceptible) recipients with positive donors are believed to be at the highest risk.^[18,19] Our lone patient with PTLD was EBV negative pretransplant. His donor’s EBV status was unknown. Our protocol is now modified to include donor’s EBV and CMV IgG titers.

Coronary allograft vasculopathy

This is a much-feared complication of transplant and leading cause of death long term. Its incidence is 13%, 25%, and 54% at 1, 5, and 10 years posttransplant.^[20-22] Our four patients with CAV (Grade 1) were placed on daily mammalian target of rapamycin kinase inhibitors everolimus or sirolimus instead of mycophenolate. All our transplant patients are placed on rosuvastatin posttransplant. We have now changed our protocol to include coronary angiography at the 1-month biopsy as well to delineate donor-derived coronary disease in donors older than 40 years. This will also allow us to

identify “rapidly progressive CAV” which carries an exponentially higher mortality.^[23]

Pancreatic pseudocyst

Pancreatic pseudocyst is a known complication postorgan transplant.^[24,25] The pancreatic pseudocyst in our patient was presumed to be a complication of previous episodes of asymptomatic/chemical pancreatitis, perhaps resulting from immunosuppression.

Infections

Infections were not a major morbidity in our cohort, beyond 1 month posttransplant. Our experience of 20% infection rate (bacterial) immediately posttransplant is consistent with published data.^[26] Our instructions to families are to minimize visitors to zero for a month postdischarge home and to minimize stepping out of the house for the first 6 months. School going children are encouraged to home school for that period. The diet for immunosuppressed patients is followed for the first 12 months posttransplant. These may have been factors in reducing infection rate in our cohort.

Hyperlipidemia

Hyperlipidemia is prevalent in 60%–80% of posttransplant patients. Statins may help with hyperlipidemia and also increase in survival posttransplant, reduction in rate of rejection, PTLT, and CAV.^[27,28] We place all our transplant patients on rosuvastatin posttransplant.

Limitations of the study

Small cohort size, retrospective data collection and missing data points, insufficient long-term follow-up, and an evolving management protocol are the limitations of the study. It is also beyond the scope of this study to discuss the economics of heart transplant in our setting of a limited resource country.

CONCLUSION

The results suggest acceptable short-term outcomes in Indian pediatric patients after heart transplantation in the current era. Significant rejection episodes and CAV need careful follow-up as do concerns of infections in the long term.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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