Clinical recommendations for postoperative care after heart transplantation in children: 21 years of a single-center experience

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Heart transplantation is an option for children with complex congenital heart disease and cardiomyopathies. A patient's quality of life and long-term survival depend on successful management of the surgical complications and adverse side effects of immunosuppression. The purpose of this review was to summarize the practical management of postoperative care in this patient population and to make recommendations for the future.

KEYWORDS: Heart Transplantation; Children; Immunosuppression; Rejection; Postoperative Care.

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INTRODUCTION

Heart transplantation is a therapeutic option for complex congenital heart disease and treatment-refractory cardiomyopathies. Some of the factors that affect the success of this procedure were reviewed, including the indication criteria for recipients and donors, immediate postoperative management, immunosuppression, complications and survival.

The main indications for heart transplantation are as follows: severe ventricular dysfunction despite optimized drug therapy in patients with cardiomyopathies or who have undergone corrective surgery for congenital heart disease; treatment-refractory malignant arrhythmias; complex congenital heart disease not surgically repaired; unresectable cardiac tumors causing ventricular outlet obstruction; unacceptable quality of life; heart failure stages C and D; oxygen consumption less than 50% predicted for age; and progressive pulmonary hypertension that prevents heart transplantation (1-3).

The principal indications for transplantation in congenital heart disease are as follows: hypoplastic left heart syndrome with right ventricular dysfunction; pulmonary atresia with significant obstructive anomalies of the coronary arteries; interrupted aortic arch with severe subaortic obstruction; severe unbalanced atrioventricular septal defect; various single ventricle defects with subaortic obstruction; and severe Ebstein's anomaly. Dilated cardiomyopathies occur most frequently, followed by restrictive cardiomyopathies (1-6).

The contraindications for heart transplantation are the following: uncontrolled systemic infection and sepsis; irreversible pulmonary hypertension despite pulmonary vascular reactivity tests; multiple organ failure; complex genetic syndromes; severe central nervous system abnormalities; psychiatric disorders; prematurity; uncontrolled malignancy; and progressive systemic disease with early mortality (genetic, metabolic and mitochondrial syndromes) (1-4).

The preoperative evaluation includes the determination of the pulmonary vascular resistance index. Children with pulmonary vascular resistance indices greater than 6 Wood units/m^2 are more susceptible to the development of right ventricular dysfunction and mortality. Currently, inhaled nitric oxide and sildenafil citrate are administered postoperatively to reduce the risk of pulmonary hypertension crises (7-10).

The donor's weight is another important consideration. It is recommended that the donor weigh up to three times as much as the recipient (11). If the donor weighs more than the recipient, the latter may develop a syndrome characterized by hypertension, elevated intracranial pressure and altered consciousness due to the higher stroke volume of the donor's heart (11).

Ischemic time must be carefully monitored; ischemic times greater than three to four hours are associated with

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high mortality in the first 30 days because of primary graft failure (11-13).

The panel reactive antibody (PRA) test indicates the percentage of the recipient's antibodies that react with human leukocyte antigen (HLA), and patients with elevated PRA scores are termed ''sensitized''. Therefore, it is crucial to review the medical histories of both the donor and the recipient, including blood product transfusions and previous procedures (14-15). After the transplantation team has been notified of a potential donor, a virtual crossmatch between the recipient and donor is performed, and the transplantation procedure begins, according to the results of crossmatch.

During the immediate postoperative period, the main complications are primary graft failure, right ventricular failure, pulmonary hypertension crisis, rejection and infection.

The primary objective in the immediate postoperative period is maintaining adequate cardiac output because of denervation and ischemic time. The dependence on vasoactive drugs occurs mainly in the first days post-transplantation; it is recommended that these drugs be administered by continuous infusion during the first 72 hours after surgery (11). The vasoactive drugs of choice are dobutamine, milrinone, Isuprel and epinephrine (11). The following parameters should be monitored during the administration of vasoactive drugs: temperature, heart rate, respiratory rate, blood pressure, central venous pressure, left atrial pressure, mean pulmonary artery pressure, urine output and venous oxygen saturation.

Primary graft failure is a major cause of immediate mortality (prior to 30 days) after heart transplantation (15). The treatment consists in some cases the use of mechanical circulatory support or retransplantation. Prolonged ischemic time is a primary risk factor for primary graft failure (2).

Pulmonary hypertension can be assessed by measuring the pulmonary artery pressure and the right atrial pressure. Right ventricular dysfunction and tricuspid regurgitation secondary to pulmonary hypertension can be monitored with echocardiography. Drugs such as non-selective systemic vasodilators (sodium nitroprusside) and inhaled nitric oxide (in selected cases) are used in combination with inotropic drugs, such as dobutamine and milrinone. Milrinone reduces pulmonary and systemic vascular resistance and provides non-adrenergic inotropic support. In cases of severe right ventricular failure, extracorporeal membrane oxygenation may be indicated, but it increases the risk of bleeding and neurological complications (15-20).

Patients with chronic congestive heart failure may exhibit elevated systemic vascular resistance, which can lead to paradoxical hypertension in the postoperative period. Sodium nitroprusside and angiotensin inhibitors are drugs used to manage systemic hypertension (15).

Hypertension caused by cyclosporine may develop in the first weeks to months after transplantation, independent of nephrotoxicity. This complication may even occur years later and cause worsening renal function. The mechanisms of cyclosporine-induced hypertension remain unclear. Some studies have reported hypertensive patients with no renal function changes (11,15).

Prophylactic therapy is used to prevent bacterial, cytomegaloviral (CMV), toxoplasmosis and fungal infections (21-22). The choice of immunosuppressive regimens varies among transplant centers. Immunosuppression protocols for children may or may not include corticosteroids. A triple (calcineurin inhibitor, cytostatic agent and steroids) or double regimen (calcineurin inhibitor and cytostatic agent) may be employed, with or without induction therapy with antithymocyte globulin.

The most common calcineurin inhibitors are cyclosporine and tacrolimus. Cyclosporine is initiated preoperatively and discontinued during the cardiopulmonary bypass; after surgery, it is then readministered intravenously at a continuous dose of 0.1 mg/kg/h until the endotracheal tube is removed from the patient. Following tube removal, pediatric patients are administered oral cyclosporine at an initial dose of 5 mg/kg/day, which is adjusted according to the serum cyclosporine level, which is normally between 250 and 300 ng/ml. In patients with cyclosporine toxicity, tacrolimus is administered at oral dose of 0.15 to 0.3 mg/kg/day (14). Branco et al. (23) reported good outcomes after converting from cyclosporine to tacrolimus in cases of toxicity and refractory rejection of cyclosporine.

A cytostatic drug, such as azathioprine, is administered at a oral dose of 1 to 3 mg/kg/day. The total number of leukocytes is then monitored; a value greater than 4000 cells/mm^3 is required. Mycophenolate may be administered instead of azathioprine. Mycophenolate acts by inhibiting the proliferation of lymphocytes; it can lead to bone marrow suppression. The main side effect is gastrointestinal symptoms.

In addition to cytostatic agents and calcineurin inhibitors, thymoglobulin and methylprednisolone are commonly administered. The methylprednisolone dosage is based on the child's weight.

The main complications that can occur post-transplantation are described below.

REJECTION

Acute rejection is the most common complication of transplantation. Its incidence is high during the first four months post-transplantation. Endomyocardial biopsy is a diagnostic method that shows the degree and type of rejection (24). However, acute rejection in children is commonly diagnosed using noninvasive methods (2,25); such as clinical symptoms, conventional electrocardiogram, Doppler and tissue echocardiography, gallium-67 scintigraphy and BNP levels. The clinical signs of acute rejection include cardiac arrhythmias and symptoms of congestive heart failure, along with nonspecific signs, such as irritability and anorexia (14). An electrocardiogram showing a decrease in the sum of the QRS voltages greater than 20% may indicate acute rejection. Echocardiography may also show ventricular dysfunction, increased cavity diameter, septum and posterior wall thickness, atrioventricular valve insufficiency, pericardial effusion and changes in ventricular diastolic function.

The treatment for acute rejection consists of maintaining the rejection immunosuppression regimen (14). In patients with stable hemodynamic parameters, methylprednisolone is administered for four days. In cases in which the child needs vasoactive drugs and ventricular dysfunction is demonstrated by echocardiography, antithymocyte globulin preparation is administered in addition to methylprednisolone. Antithymocyte globulin is used for seven to ten days, and it is monitored by measuring the level of T lymphocytes in the peripheral blood; the requirement is fewer than 150 cells/mm^3 by flow cytometry.

Irradiation of lymphocytes (ILT) and methotrexate are used as rescue therapeutic options in patients with refractory rejection.

Humoral rejection is diagnosed by microscopic and immunofluorescence analyses of endomyocardial biopsy specimens (24). Immunofluorescence findings may also indicate immunoglobulin and complement deposition in the vascular endothelium and evidence of endothelial cell swelling. Humoral rejection is associated with sensitized patients, high mortality, graft vascular disease development and poor survival (12,15,24). Treatments for humoral rejection include methylprednisolone, cyclophosphamide, immunoglobulin, rituximab and plasmapheresis (12,15).

Hyperacute rejection is a form of humoral rejection that occurs immediately after transplantation and is mediated by preformed antibodies (15). These antibodies result from previous exposure to human antigens (e.g., during pregnancy or blood transfusions), and they act directly against antigens in the transplanted heart. Patients with hyperacute rejection have poor prognoses and usually require assisted circulation because of severe ventricular dysfunction.

INFECTION

The infectious process represents a major cause of death in the first year after transplantation. Schowengerdt et al. (21) reported that among 332 patients undergoing heart transplantation, there were 276 episodes of infection: 164 (60%) bacterial, 51 (18%) CMV, 19 (7%) fungal and 7 (2%) protozoal. Bacterial infections occur more commonly in children under six months of age at transplant, comprising 73% of all infections in this age group, compared with 49% in children older than six months. The highest incidence of bacterial infection occurs during the first month after transplantation. The most common infections are bronchopneumonia and bacteremia. CMV is responsible for 59% of all viral infections, with the highest risk in the first two months after transplantation. Factors associated with CMV infection include age, mechanical ventilation, CMV serologic status disparity (a positive donor and a negative recipient) and prolonged ischemic time.

HYPERTENSION

Hypertension is a frequent complication, occurring in approximately 60% of patients within five years after transplantation (4).

GRAFT VASCULAR DISEASE

Graft vascular disease, one of the main factors limiting long-term survival, may be related to both immunological and non-immunological factors. Dobutamine stress echocardiography has been used as a noninvasive diagnosis method; however, coronary angiography and intravascular ultrasonography are currently the methods of choice. The potential risk factors for graft vascular disease are older age and an increased number of rejections (25-29).

TUMOR

The occurrence of tumors after heart transplantation is termed post-transplant lymphoproliferative disease. These tumors are predominantly of a B cell lineage and are usually triggered by Epstein-Barr virus. This disease may occur in 5% of patients within five years after transplantation (25,29).

RENAL COMPLICATIONS

Nephrotoxicity can be caused by the chronic use of calcineurin inhibitors. Patients may develop severe renal failure, which is defined as the need for dialysis or transplant (15,28).

DYSLIPIDEMIA

Dyslipidemia is a common complication after cardiac transplantation. Studies have produced conflicting results regarding the association between dyslipidemia and immunosuppressive drugs in children (15,23).

SURVIVAL

As reported in the twelfth official pediatric registry of the International Society for Heart and Lung Transplantation (ISHLT) (28), the median patient survival depends on the patient's age at the transplant. In our setting, 133 patients (4 were young adults) underwent transplantation, and five underwent re-transplantation. Eighty-five patients were alive from October 30, 1992 to November 3, 2013.

AUTHOR CONTRIBUTIONS

Azeka E conceived the study, assisted with its design, wrote the manuscript and revised and approved the final draft. Jatene MB, Tanaka AC, Galas FR, Hajjar LA, Miura N and Auler Junior JO conceived the study, assisted with its design and performed the data analysis and interpretation.

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