PAPERS AND SHORT REPORTS

Cardiac transplantation in severely ill patients requiring intensive support in hospital

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Abstract

Sixty four patients were referred for cardiac transplantation from a single cardiac team at this hospital between October 1984 and December 1986. Of these patients, 33 were referred for urgent transplantation, all of whom required intensive treatment in hospital with intravenous infusions of cardiac drugs, intra-aortic balloon counterpulsation, peritoneal dialysis, ventilation, or any combination of these to sustain life. Of these 33 patients, six died while awaiting transplantation, one was removed from the waiting list for a transplant, and 26 received cardiac transplants. There were five deaths within 24 hours of operation and one death 10 days after the operation. Twenty of those who had surgery had a successful outcome of transplantation, but there was one late death 10 weeks postoperatively and a further death 31 months after surgery. Eighteen patients were alive and well 10 to 33 months (mean 19.4 months) after transplantation, with an overall survival rate after surgery of 69%.

Provided that surgery can be performed before renal failure has progressed such that renal transplantation is necessary, the results are excellent (surgical survival 85.5%) and, we believe, justify the expenditure and staffing requirements necessary to treat these terminally ill patients.

Introduction

With the introduction of cyclosporin as an immunosuppressive drug¹ and the modification of immunosuppressive regimens^{2,3} there has been a pronounced improvement in the results of transplanta-

tion.⁴ Greater numbers of operations are being performed each year, and increasing numbers of patients are being referred and accepted for surgery. Many of these referred patients have terminal cardiac failure, some with secondary end organ damage, and require intensive management to sustain life. The early results of transplantation in these critically ill patients are encouraging,^{5,6} and the policy of this unit has been to give intensive treatment until a suitable donor heart becomes available.

Given the shortage of donor organs, as experienced by most centres, providing these patients with a transplant will lead to a shortfall in donor organs for those who are awaiting "elective" transplantation. It is therefore essential to evaluate critically the results of this policy. We have reviewed our experience with these patients to assess the short and medium term outcome (<34 months) and attempt to identify factors which could influence prognosis.

Patients and methods

All patients who were referred for urgent cardiac transplantation from a single unit at this hospital between October 1984 and December 1986 were included in the review. All had end stage cardiac failure that was not amenable to medical treatment or persistent ischaemia associated with poor left ventricular function and were dependent on intensive management in hospital requiring at least one intravenous infusion of a cardiac drug to maintain an adequate cardiac state before transplantation. General contraindications to cardiac transplantation included a high pulmonary vascular resistance (>8 Wood units) and other severe irreversible organ disease not related to primary myocardial failure. One young patient underwent urgent transplantation, however, despite having a high pulmonary vascular resistance. The presence of severe renal or hepatic dysfunction, if considered secondary to myocardial failure, did not militate against subsequent transplantation. A recent pulmonary infarction was not regarded as a contraindication to transplantation.

All patients were investigated fully where possible, with left and right heart catheterisation with or without myocardial biopsy in addition to the standard non-invasive investigations (electrocardiography, radiology, echocardiography, and radionuclide ventriculography). In some cases, however, myocardial decompensation was so severe that invasive investigations were contraindicated. In these cases two dimensional echocardiography was used to show the poor myocardial contractility.

A full metabolic and haematological profile was performed regularly to

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assess end organ damage and to help to decide on further intervention. Patients were classified as having normal, mild, moderate, or severe renal dysfunction on the basis of their plasma urea and creatinine concentrations. We arbitrarily selected a creatinine concentration of 160 $\mu\text{mol/l}$ or a urea concentration of 14 mmol/l , or both, as the cut off point between mild and moderate renal dysfunction from our clinical experience. Severe renal dysfunction was taken as that which required renal dialysis. Liver function was assessed by hepatic enzyme estimations. For the classification, moderate hepatic dysfunction was diagnosed if the activities of two or more hepatic enzymes were greater than twice the upper limit of normal before transplantation or death.

Detailed screening for the early detection of infection was performed regularly and antimicrobial treatment given as required.

Medical intervention was aimed primarily at maintaining a sufficiently stable cardiac state to allow satisfactory renal and cerebral perfusion and minimise hepatic congestive damage. Intervention methods included intravenous positive inotropic agents (29 patients), intravenous nitrates (17), intra-aortic balloon counterpulsation (16), temporary right ventricular pacing (three), intermittent positive pressure ventilation (six), and peritoneal dialysis (seven). Intravenous diuretics (32 patients), antiarrhythmic agents (16), antimicrobial agents (12), and plasma protein fraction (nine) were used, as were anticoagulants, H_2 receptor blockers, diamorphine, and other drugs as required. Patients were managed on a medical ward for intensive therapy with standard monitoring facilities and individual nursing care.

Results

Of 64 patients who were referred for cardiac transplantation in the 27 months from October 1984 to December 1986, 33 patients satisfied the criteria for requiring urgent cardiac transplantation as the only viable management. There were 28 men and five women, with a mean age of 42.5 years (range 17-62 years). Thirty two patients were married, and 30 of these had families. Only one patient was unemployed before becoming ill; the others were housewives or otherwise employed.

The indication for transplantation was ischaemic heart muscle disease in 19 patients, dilated cardiomyopathy in 11, and aortic regurgitation,

FIG 1—Chest radiograph before transplantation showing pronounced cardiomegaly and interstitial pulmonary oedema. A sternal wire is visible from previous coronary artery bypass surgery.

transient myocardial ischaemia with poor left ventricular function, and endomyocardial fibroelastosis in one patient each. The severity of cardiac dysfunction was shown in the results of radionuclide ventriculography, performed in 16 instances, with a mean left ventricular ejection fraction of 12% (range 6-20%).

Twenty six patients received cardiac transplants, and six died awaiting transplantation. One patient was withdrawn because of having suffered a stroke. Of the 26 transplants, 23 were orthotopic and three were heterotopic. There were five deaths within 24 hours of transplantation and one death 10 days after surgery. Of those who received transplants, 20 left hospital. On an intention to treat basis this represents an early success rate of 60.5% for the

group as a whole. There was one late death 10 weeks after surgery, and a further patient died 31 months after transplantation. Seven patients were alive after more than two years; 18 patients were alive at a mean of 19.4 months after transplantation (range 10-33 months).

The total number of days in hospital before transplantation or death was 840, with a mean stay of 25 days (range 1-135 days), though many had previously been inpatients at other centres before referral. The mean duration of hospitalisation for those who died awaiting transplantation was 34 days and for those with a successful outcome of surgery 27 days. The

FIG 2—Chest radiograph in the same patient soon after transplantation showing slight cardiomegaly and clear lung fields.

group of patients who died in the early postoperative period on the whole received suitable donor hearts at an earlier stage. This was, however, a reflection on their critical state, these patients almost invariably requiring considerable interventional support.

The intravenous infusions included dopamine, dobutamine, adrenaline, noradrenaline, isoprenaline, aminophylline, and nitrates. A mean of three intravenous infusions was given per patient (range 1-6). Those with a successful outcome had a mean of 2.6 infusions; those who died waiting had a mean of 3.37 infusions and those dying in the early postoperative period a mean of 3.66 infusions.

Sixteen patients had normal or near normal renal parameters as assessed by plasma urea and creatinine concentrations. Of the 16 patients, 14 had a successful result of transplantation. Five of 10 patients with moderate renal dysfunction (mean plasma urea 28.5 mmol/l ; mean plasma creatinine 213 $\mu\text{mol/l}$) had a successful outcome. Seven patients required peritoneal dialysis, and all except one died either while waiting for a suitable donor (two patients) or in the early postoperative period (four patients).

Twenty eight patients had abnormalities of hepatic enzymes. Nineteen patients had normal or mildly abnormal hepatic function, 14 of whom had a successful result of transplantation. Of 14 patients with moderate hepatic dysfunction, six underwent successful transplantation.

Sixteen patients required insertion of an intra-aortic balloon pump, and six had a successful result. One of these patients, however, died 10 weeks after surgery. Six patients required a combination of intra-ortic balloon counterpulsation and peritoneal dialysis, and one of five patients who received a transplant had a successful outcome.

Although proved or suspected infection was relatively frequent, especially in those who required multiple access lines and catheters, this usually responded well to standard antibiotic regimens. Infection which was thought to be a contraindication to early transplantation was encountered on only two occasions and was successfully treated on one. For 23 patients 24 hour Holter monitoring was performed, and 11 of these had short episodes of ventricular tachycardia. Sixteen patients received amiodarone or lignocaine for arrhythmias.

Intermittent positive pressure ventilation (six patients) was, as expected, associated with a poor prognosis, as was cardiopulmonary resuscitation, though three patients who had cardiac arrests subsequently underwent successful transplantation, and another patient, who could not be weaned off cardiopulmonary bypass after redo coronary artery bypass surgery despite maximal support, received a heterotopic cardiac transplant 12 hours later, with a good result.

Of seven patients with proved or clinically suspected pulmonary

embolic episodes before surgery, six underwent successful transplantation, and five had a successful result.

All 18 surviving patients were reviewed in October 1987 to assess quality of life. Five categories were used: very poor, poor, fair, good, and excellent. Sixteen patients were reported to have an excellent (12) or good (four) quality of life; two had a fair quality of life, one being restricted by postherpetic neuralgia. No patient was greatly restricted by cardiac symptoms. Seven patients were in full time employment, a further three were seeking gainful employment, and one other had retired (aged over 60 years). Three further patients were working full time as housewives; two had young families. The remaining four patients were not seeking employment.

Discussion

Until relatively recently all patients with end stage cardiac failure invariably died of their disease, but the results of cardiac transplantation have improved appreciably in recent years and thus it is a successful approach to treating such patients. The one year survival is about 80%.^{7,8} The actuarial survival curves for all patients who underwent orthotopic cardiac transplantation from 1978 through 1985 and were registered at the International Registry for Heart Transplantation showed an actuarial survival rate of 76.6% at five years after heart transplantation when treated with cyclosporin.⁴ Similar figures have been found by other groups.^{9,10}

With the success of this therapeutic intervention, and the appreciable increase in the number of transplant operations being performed⁴ greater numbers of patients are being referred for consideration for possible cardiac transplantation. Many of these have terminal cardiac failure and require intensive management in hospital to sustain life.⁵ Urgent cardiac transplantation is the only treatment option.

The patients described in this study pose a difficult management problem as a decision not to accept them for urgent transplantation will almost certainly lead to early death. All those who did not receive a heart transplant died at a mean of 34 days after admission. By conventional selection criteria, however, many of these patients would not be considered ideal candidates for transplantation because of their critical state and the development of end organ dysfunction related to the poor cardiac function. With a broadening of selection criteria in some centres in recent years, however, these patients are undergoing transplantation, and the early results are encouraging. Because of the potential of this procedure to return these critically ill patients to a normal life our policy has been to give patients intensive treatment while waiting for a suitable donor heart. Applying this policy on an intention to treat basis, we have had an early success rate of 60% and a late success rate of 54.5% with this group of patients, a mortality at operation of only 19%, and a success rate of 85.5% for surgery in those patients who did not require renal dialysis. These figures reflect the benefits of this intervention in patients whose early death is expected. As the results of surgery are only slightly worse than in the "elective" group, the moral issue of using sparse donors and resources is not as acute as originally expected.

With the increased awareness of the benefits of transplantation it is hoped that more patients will be referred for consideration for transplantation before end organ dysfunction develops or support in hospital is needed. This is not always possible, as patients who are apparently healthy may deteriorate rapidly. An adequate supply of suitable donors is essential, otherwise many of these "electively" referred patients will deteriorate to the critically ill state while on the waiting list.

In reviewing our experience with patients who have terminal cardiac disease we have identified factors that indicate a poor ultimate prognosis. The most important is the delay before receiving a transplant. The presence of severe renal dysfunction, with or without renal replacement, and the requirement of multiple inotropic support and intra-aortic balloon counterpulsation all reflect the final failure of the heart to function adequately as a pump and suggest a poor eventual outcome if transplantation is delayed.

Mild hepatic dysfunction did not seem to affect the outcome of transplantation in our patients. The requirement for multiple

indwelling catheters led to an increased incidence of infection. With regular screening, however, we were able to diagnose infection early, and most episodes were easily managed with standard treatment regimens.

Assessment by invasive procedures of some of these patients before acceptance for transplantation was deliberately limited owing to their poor clinical conditions. Two dimensional echocardiography showed such poor myocardial contractility that it was thought that cardiac catheterisation would contribute little to further management. Indeed, four patients deteriorated rapidly after cardiac catheterisation, two having a cardiopulmonary arrest. All had such poor cardiac reserve, with virtually no possibility of a return of adequate cardiac function, that many of these investigations only helped in the diagnosis but did not contribute further to management. In the patients with overwhelming cardiac failure coronary angiography and left ventriculography did not affect our decisions on management. Right heart catheterisation was important to assess the degree of pulmonary vascular resistance.

Our experience with patients undergoing transplantation who have had a recent suspected or proved pulmonary infarction is similar to that of Young *et al.*¹¹ These patients appear to do well after transplantation, though clearly the potential for secondary infection exists.

With the appreciable improvement in survival figures we thought that the selection criteria should be broadened and so enable patients with overwhelming cardiac failure with or without secondary multisystem dysfunction to be considered for transplantation. We have outlined many problems, but, provided the patients survive the pretransplantation phase without requiring renal dialysis while awaiting a suitable donor, it appears that at least in the early stages they do almost as well as those who are electively assessed and given a transplant.

Clearly, these critically ill patients require considerable resources—not only medical and nursing personnel—but also drugs and medical equipment. We believe our results justify the use of these resources, especially as many patients are young and have young families to support, and many have returned to work after transplantation. The results were less good in patients who required a combination of intra-aortic balloon counterpulsation and renal dialysis. More recently we have used the intra-aortic balloon pump earlier in the clinical course and have had a reduced requirement for renal dialysis.

Cardiac transplantation has become a successful definitive treatment for patients with advanced cardiac failure. The waiting period in these patients after acceptance for transplantation is a major incremental risk factor, however. Early transplantation obviates the need for prolonged intensive support with all its associated problems. This reflects on the need for an increase in the use of available donors, and continuing education of both the public and the medical profession is of paramount importance.

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