Plasmapheresis on Cardiopulmonary Bypass

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Abstract

Patients waiting for heart transplantation with positive cytotoxic antibody screens are at high risk of acute or chronic immunological damage of the recipient organ. A highly sensitised patient is defined as one whose Panel Reactive Antibody levels (PRA 's) are in excess of 10% (normal 0%). The pre-formed anti HLA antibodies are an important cause of acute cellular and vascular rejection post-transplant. Sensitisation may occur as the result of exposure to multiple previous blood products. Ideally a donor should be selected to whom the recipient has no pre-formed antibodies (negative T and B cell cross-match) but this is frequently not realistic or achievable. We have used plasmapheresis to treat a highly positive PRA patient whilst on cardiopulmonary bypass (CPB). This was performed using a Gambro PF1000N plasmapheresis filter connected to our routine CPB circuit in a similar fashion to our routine haemofilter system. Three plasma volumes were exchanged while on CPB with a declining schedule for the next month in conjunction with aggressive B-cell immunosuppressive therapy. Intraoperative plasmapheresis can be used for patients that would otherwise not receive transplantation due to elevated PRA's.

Introduction

Highly sensitised patients are generally those who have had previous cardiac surgeries which have involved foreign matter eg grafts, valves and/or blood transfusions. Antibodies are formed to this foreign material. The nondonor specific panel reactive antibody assay (PRA) provides initial screening for sensitisation of the patient who may have anti-HLA antibodies with an estimated incidence of 11-15% of listed cardiac transplant patients (1). This can increase when ventricular support devices are used to an overall positive PRA incidence of 66%. Plasmaphresis is the process of removing plasma from the blood whilst a replacement product is simultaneously infused. For a transplant recipient this process is required to remove antibodies that have the potential for hyperacute antibody mediated rejection as a consequence of reperfusing the donor heart. The volume to be exchanged is calculated from two-thirds of the total blood volume. For removal of antibodies a double exchange is recommended, which is usually done via a femorally placed vascath in ICU, if patient is stable & time constraints allow. However due to the practical aspects of retrieving a donor organ & these patients coming from distant locations, in combination with haemodynamic instability, plasmapherisis during CPB before X-Clamp removal (ie such that donor organ is exposed to minimal donor specific antibodies) is the most practical option.

Method

Currently on our transplant waiting list there are several children with high PRA levels > 10%. We had a 15.3 year old, 65 kg, 180 cm male with the following diagnosis present for heart transplantation;

- Left atrial isomerism
- Double outlet right ventricle
- Complete AVSD with hypoplastic left ventricle
- Pulmonary artery band (1993)
- Kawashima procedure (1994) with RV to aortic conduit
- Conduit change (1996) with AV valvuloplasty.
- Further conduit change (1999) with 19 mm Homograft.
- Atrial re-entry tachycardia
    - Tachycardia induced cardiomyopathy
    - Dual AV nodes.
    - Insertion of permanent cardiac pacemaker (16/12/2003)

The Plasmapharesis volume exchanged was based on the body weight of the patient with 2-3 blood volumes required. The filter should be rinsed with at least 2 litres of plasmalyte 148 prior to connection to CPB circuit, with a target flow of 80-130 ml/min. The patient's plasma volume was initially exchanged with 3 litres of RCH plasmapharesis replacement solution;

Ingredients	1 Litre	2.64 Litre
Potassium Di-Hydrogen Phosphate K 1 mmol / mL PO_4 1 mmol / mL	1.5 mL	3.96 mL
Potassium Acetate 2.45g in 5 mL K 5 mmol / mL Acetate 5 mmol / mL	0.4 mL	1.06 mL
Sodium Chloride 20% Na 3.42 mmol / mL Cl 3.42 mmol / mL	27.66 mL	73.11 mL
Calcium Chloride.$2H_2O$ 0.74g /5 mL Ca 1 mmol / mL Cl 2 mmol / mL	2 mL	5.29 mL
Dextrose 50%	6 mL	15.86 mL
Magnesium Chloride 0.48 g in 5 mL Mg 1 mmol / mL Cl 2 mmol / mL	0.7 mL	1.85 mL
Sodium Bicarbonate 8.4% Na 1 mmol / mL HCO_3 1 mmol / mL	25 mL	66.1 mL
Sodium Acetate 1.63 g in 10 mL Na 2 mmol / mL Acetate 2 mmol / mL	3.58 mL	9.46 mL
Normal Serum Albumin 20% 20 g in 100 mL (Human)	150 mL	396.5 mL
Water for Irrigation	783.16 mL	2070 mL

then 28 units (8.4 litres) of fresh frozen plasma (FFP) with 12 litres of filtrate removed. The plasmapharesis filter was then swapped with a standard haemofilter & 65 g (1.1L) of Intragam (IgG) administered all of which had to be completed before X-Clamp removal and took approximately 3 hours.
CPB was urgently instituted femorally due to massive blood loss via sternotomy, with plasmapharesis started once CPB was initiated and patient stabilised. CPB was undertaken in a routine fashion as per Royal Children's Hospital protocol (1) for a patient of this size using a Terumo Capiox RX15 W40 oxygenator.
To minimise the effect of anaesthetic and element (eg Ca^{++}) washout during plasmapharesis, isoflurane of 2% was maintained into the ventilating gas of the oxygenator & a calcium infusion of 10-20 mmol/hr with 2 mmol Ca++ boluses per bag of FFP. Blood gases were performed every 15 minutes as well as continuous blood gas analysis via the CDI500. Measured parameters were kept within the normal range and a TEG performed prior to CPB discontinuation was also within normal ranges.

Results

With increasing numbers of patients whose PRA's > 10% are requiring heart transplantation a major concern is being able to accurately identify antibodies to expedite there chance of

receiving transplantation. The multiplex Luminex system was used for screening and antibody identification. Molecular reactions take place on the surface of microsphere sets that have been colour coded using a blend of different fluorescent intensities of two dyes. The microsphere acts as molecular carriers that capture a sample and then are tagged with a fluorescently labelled reporter tag that binds to the captured sample on the microsphere. The microspheres are then injected into the device using microfluidics to align them in single file, where they pass through two lasers. One laser illuminates the colours inside the microsphere to identifiy which bead is being read and the second laser excites the colour on the bead surface. Digital signal processing translates the signals into real time and quantitates the data for each reaction.
The patient prior to transplantation had extremely high donor specific antibodies (which was identified post transplantation) however post CPB plasmapheresis, all cytotoxic antibodies were considered negative (< 500 mfi). However at later time points after plasmapheresis in ICU and the ward, antibody levels had returned to pre transplant levels (see figure 1).

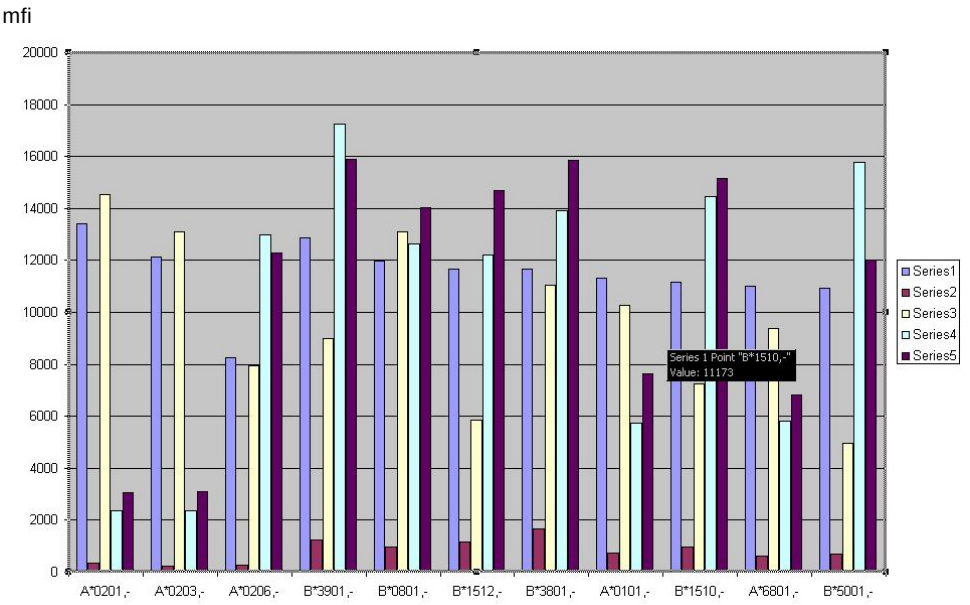

Figure 1

Discussion

Transplant recipients who have preformed antibodies to major histocompatability complex determinants or who develop antibodies post transplant have a higher incidence for long term rejection, vascular disease and lower survival rates (1-4,5). Plasmaphoresis has been shown to be efficacious if performed preoperatively (6) and intraoperatively (7).

We were able to demonstrate that plasmapheresis can be combined with the CPB circuit and effectively remove cytotoxic antibodies in a PRA patient. Perhaps with our experience it may be safer to do this procedure on haemodynamically unstable patients on bypass. However you must remain aware of the removal of serum factors and actively monitor and replace anaesthetic agents, heparin and calcium.
A 2 to 3 volume exchange over 3 hours is possible because of the higher flows rates achievable with CPB, which may also aid in maintaining patient haemodynamic stability during the procedure.

Because of potential B-cell response to the transplanted heart, plasmapheresis along with B-cell specific immunosuppressant therapy may decrease the risk of rejection. The frequency and volumes of plasmapheresis post transplant should be based on the PRA results.

The plasmaphoresis filter is connected to our CPB circuit in the same way as our haemofilter. The inlet line to the filter originates from the recirculation line of our CPB circuit and passes through a Jostra RP100 roller pump. This allows precise control of the blood flow through the filter. The effluent line is placed under a vacuum of -50mmHg to increase the Trans Membrane Pressure and facilitate the removal of the plasma. The outlet of the filter then returns the blood to the venous reservoir.
It is worth noting the importance of pre wetting the filter fibres with two litres of crystalloid solution prior to it being used. This is to avoid the increased incidence of haemolysis from the non wetted fibres and to flush out any excess material from the manufacturing process.

References

1. Loh E. Bergin JD, Couper GS et al. Role of panel-reactive antibody cross-reactivity in predicting survival after orthotopic heart transplantation. J Heart Lung Transplant. 1994; 13:194-201.

2. Kerman RH, Orosz CG, Lorber MI. Clinical relevance of anti-HLA antibodies pre and post transplant, AM J Med Sci. 1997;313:275-78.

3. Kerman RH, Kimball P, Scheinen S,et al. The relationship among donor-recipient HLA mismatches , rejection and death from coronary artery disease in cardiac transplant recipients. Transplantation. 1994;57:884-88.

4. Kobabashigawa JA, Sabad A, Drinkwater D et al. Pretransplant panel reactive antibody screens. Are they truly a marker for poor outcome after cardiac transplantation? Circulation. 1996;94:11294-97.

5. Smith JD, Danskine AJ, Laylor RM et al. The effect of panel reactive antibodies and the donor specific cross-match on graft survival after heart and heart/lung transplantation. Transplant Immunol. 1993;1:60-65.
6.Robinson JA, Radvany RM, Mullen MG et al. Plasmapheresis followed by intravenous immunoglobulin in presensitised patients awaiting thoracic organ transplantation. Therap Apheresis. 1997;1:147-51.

7. Larson DF, Elkund DK, Arabia F et al. Plasmapheresis during cardiopulmonary bypass: A proposed treatment for presensitised cardiac transplantation patients. 1999;31:177-83.