Case Report

Simultaneous Therapeutic Plasma Exchange in Parallel with Cardiopulmonary Bypass for Prevention of HLA-Antibody Mediated Rejection in a Pediatric Double-Transplant Patient

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Therapeutic plasma exchange (TPE) has been used peri-operatively to prevent antibody-mediated rejection (AMR) in pre-sensitized solid organ transplant patients. Intraoperative TPE during cardiopulmonary bypass (CPB) has been reported in neonates receiving ABO-incompatible cardiac transplants, as well as in adults undergoing cardiac surgery. To our knowledge, intraoperative TPE in parallel with CPB (TPE-CPB) for prevention of human leukocyte antigen (HLA)-AMR has not been reported in pediatric cardiac transplantation. A 13 year old female with dilated cardiomyopathy, status post orthotopic cardiac transplant at 5 months of age, presented for cardiac re-transplantation due to end-stage heart failure and renal transplantation for end stage renal disease. Histocompatibility testing was weakly positive for antibodies to HLA-DQ6, with weakly positive donor crossmatch. In order to minimize ischemic time of the donor heart, TPE was performed while on CPB, immediately prior to cardiac transplantation. Apheresis machine access and return lines were connected via stopcocks to the CPB via proximal and distal ports, respectively, on the venous/low pressure side of the CPB circuit, before the CPB pump and oxygenator. The apheresis access line pressure alarm was set to 10 mm Hg less than the CPB pump pressure, to avoid pressure alarms and apheresis pump shutdown. The procedure was well tolerated, without complications. The subsequent renal transplant was uneventful. Post-operatively, no AMR was seen, and the patient continues to have good cardiac and renal function. Intraoperative TPE-CPB is feasible and safe, and may be considered for reduction of HLA antibody level immediately prior to cardiac transplantation in pediatric patients.
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Key Words: *therapeutic apheresis, cardiopulmonary bypass, antibody-mediated rejection, HLA-allosensitization, cardiac transplant*

INTRODUCTION

Antibody-mediated rejection (AMR) in solid organ transplantation can be caused by naturally-occurring anti-ABO antibodies or acquired antibodies to Human Leukocyte Antigens (HLA). AMR occurs in up to 18% of heart transplant recipients. Although the consequences of AMR have been debated, AMR has been associated with an increased risk of allograft failure, morbidity and mortality. Anti-HLA antibodies are a significant obstacle to transplantation, and are associated with rejection and increased mortality post-transplant. Post-transplantation AMR has been treated with immunosuppressive medications, intravenous immunoglobulin therapy, therapeutic plasma exchange (TPE), or a combination of these.[1,2,3]

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Given the paucity of available organs, finding a compatible organ for anti-HLA presensitized transplant recipients may be problematic. Therefore, performing TPE simultaneously with cardiopulmonary bypass (CPB) intraoperatively may offer these presensitized patients hope for successful transplantation. Technical issues to be addressed include maintaining flow in two instruments simultaneously while avoiding pressure alarm shutdown due to pressure differentials, avoiding air embolus while manipulating access lines, and anticoagulating the patient without excess anticoagulation.

The procedures also pose clinical challenges with respect to maintenance of hemodynamic stability (with pressor support) and electrolyte levels. Therefore, it is paramount for the apheresis nurse to coordinate with the perfusionist and the heart transplant team during the entire procedure.

CASE REPORT

An 80-lb 13 year old female with dilated cardiomyopathy, status post orthotopic cardiac transplant at 5 months of age, presented for cardiac re-transplantation due to end-stage cardiac failure and renal transplantation for end stage renal disease. She had been treated with tacrolimus, sirolimus, and prednisone. The current renal and cardiac transplants were donated by a single donor. The patient's crossmatch was positive for IgG antibody against the donor B-cells (not T-cells). Histocompatibility testing was weakly positive for antibodies to HLA-DQ6, which was expressed by donor cells. The mean fluorescence intensity (MFI) for HLA-DQ6 was up to 1424 (Table 1). An MFI of >1000 is scored as positive. Other HLA antibodies were not positive. No red blood cell (RBC) antibodies were detected.

In order to minimize ischemic time, TPE was performed simultaneously with CPB, immediately prior to cardiac transplantation. Intraoperative plasmapheresis was performed using a Cobe Spectra (Terumo BCT) Plasmapheresis system coupled to a CardioPulmonary ByPass pump (by Sorin) oxygenator system.

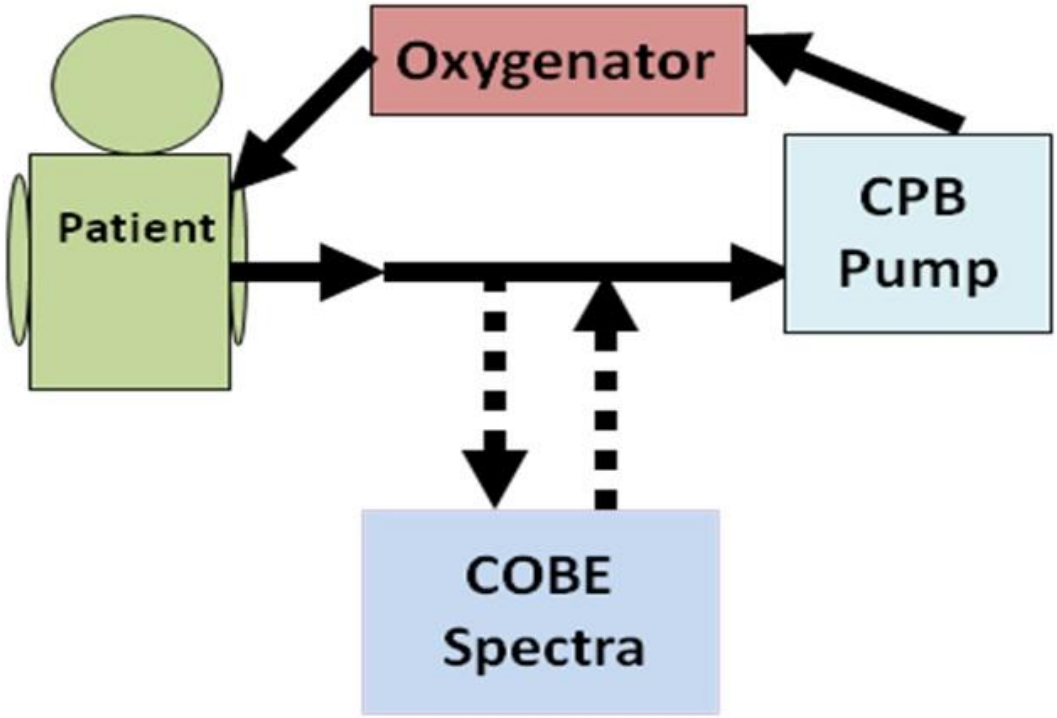

Figure 1. TPE in parallel with CPB.

The apheresis machine access and return lines were connected via stopcocks to the CPB via proximal and distal ports, respectively, on the venous / low pressure side of the CPB circuit, before the CPB pump and oxygenator (**Figure 1**). The apheresis access line pressure alarm was set to 10 mm Hg less than the CPB pump pressure, to avoid pressure alarms and apheresis pump shutdown. To avoid unnecessary over anticoagulation, the whole-blood-to-citrate anticoagulant ratio was set at 40:1. The patient and the CPB system were fully heparinized initially.

Therapeutic plasma exchange was performed, with exchange of 1.0 equivalent total plasma volume, using thawed fresh frozen plasma (FFP) as the replacement fluid. FFP was chosen as the replacement fluid due to the pre-operative measurement of mildly elevated prothrombin time of 17.7 seconds (reference range 11.5-15.0). The total processed plasma volume 1788 mL was calculated from the sum of the total plasma volume plus the CPB extracorporeal volume. Type AB FFP was selected such that ABO-compatibility was achieved for both organ donor and recipient, as this plasma carries no ABO-antibodies. The patient was AB Rh-positive, and the cardiac and renal donor was type O.

On postoperative day 1 following her cardiac transplant, the patient underwent renal transplant for chronic renal failure. Her post-cardiac transplant course was complicated by weakly positive B cell crossmatch, for which she received intravenous immunoglobulin and four rounds of TPE post-operatively. HLA antibody MFI was measured on post-operative day 5. A reduction in the HLA-DQ6 MFI was observed (**Table 1**).

The patient's initial post-transplant endomyocardial biopsies showed acute cellular rejection, but no evidence of antibody-mediated rejection. She was discharged on postoperative day 22. The patient has since been stable and recovering well on prednisone and tacrolimus with good cardiac and renal function. By seven months post-transplant there was no evidence of acute cellular or antibody-mediated rejection to the heart transplant.

Table 1. Pre- and post-transplant histocompatibility testing results.

	MFI (HLA-DQ6)
Pre-transplant	1424
Post-transplant	351

DISCUSSION

The most significant post-transplantation complications seen in allosensitized recipients are AMR and cardiac allograft vasculopathy. Often, AMR manifests with severe allograft dysfunction and hemodynamic compromise.[4] Diffuse concentric stenosis of allograft coronary arteries due to intimal expansion is a characteristic of cardiac allograft vasculopathy. Its pathophysiology is unclear but may involve chronic complement-mediated endothelial injury.[4]

Although there has been some question regarding the significance of elevated levels of preformed antibodies in patients awaiting transplantation, particularly in patients supported by ventricular assist devices, pre-transplant allosensitization increases the likelihood of AMR and cardiac allograft vasculopathy, and decreases overall allograft survival.[2,3,5] This emphasizes the importance of proper panel-reactive antibody (PRA) screening, and assignment of appropriate donor-recipient matches.[4] Recently, the use of histocompatibility testing to detect HLA-antibody specificity has been favored over PRA measurement. Our patient showed weak positivity for HLA-DQ6 antibodies, but PRA testing was not performed.

Recognizing the importance of antibody production and complement deposition in allograft endothelium as the underlying pathophysiology in AMR, mechanical removal of circulating antibodies with plasmapheresis was one of the first therapies tested on affected patients.[4]

Despite the incomplete understanding of antibody specificity and the risk of post-transplantation complications, attempts to decrease allosensitization have yielded encouraging results. The treatment of AMR in cardiac recipients is largely empirical; it is used to decrease HLA-antibody levels with varying degrees of success and includes high-dose corticosteroids, plasmapheresis, intravenous immunoglobulin, and rituximab, with the goal of B-lymphocyte depletion.

Intraoperative TPE with simultaneous CPB has been used in adult cardiac transplant patients to decrease PRA as early as 1999.[6] A few cases of patients with heparin-induced thrombocytopenia treated with TPE with simultaneous CPB have been reported.[7] In the transplant literature, successful TPE while on CPB has also been performed in infants being transplanted with ABO-incompatible donor hearts.[8] These infants appear to develop tolerance after chronic exposure to an ABO-incompatible organ in this setting. For older patients, the relative availability of ABO-compatible organs makes HLA-compatibility the premiere concern in this population. In older pediatric transplant patients with high HLA PRA, pheresis has been performed immediately pre- and post-transplant, but not simultaneously with TPE.[3]

Patient safety is our top concern for intraoperative TPE in parallel with CPB. TPE with CPB during cardiac surgery was performed safely not only in the cases mentioned above, but also in the setting of severe mechanical hemolysis.[9] Patients requiring FFP 30 minutes to 6 hours after cardiopulmonary bypass for correction of coagulation abnormalities may be at risk for potentially fatal catastrophic noncardiogenic pulmonary edema associated with marked deteriorated cardiac output. There have been no reports of noncardiogenic pulmonary edema when using FFP for TPE coupled with CPB. This may be explained by "cardiac output" being well controlled mechanically by CPB, rather than depending on biological cardiac output.

Our patient presented with pre-formed HLA-antibodies, likely a result of her prior transplants, with a weakly positive crossmatch to donor B-cells. Intraoperative TPE coupled with CPB was thus performed to decrease the level of circulating antibodies in order to minimize the risk of AMR in the immediate post-transplant period. The TPE with CPB for this patient's heart transplantation was uneventful. Four additional TPE procedures were performed daily after the heart and renal double transplantation. The patient was free of AMR to both cardiac and renal transplants seven months post-transplantation.

CONCLUSION

The pediatric cardiac transplant patient presented with pre-formed HLA-antibodies, with a weakly positive crossmatch to donor B-cells. Intraoperative TPE coupled with CPB was successfully performed in this patient during cardiac transplantation. The intraoperative TPE combined with 4 post-transplant TPE procedures resulted in a reduced level of the patient's circulating HLA antibody levels. The patient was free of AMR seven months post-transplantation.

To our knowledge, this is the first case of a pediatric double transplant patient with HLA-allosensitization in whom TPE with simultaneous CPB was used successfully during cardiac transplantation.[4,6,7]

CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.

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Not applicable.

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