ABO-incompatible heart transplants

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Abstract
A month-old baby girl with blood type O positive received a donor heart organ from a donor with blood type B. This was the first institutional ABO-incompatible heart transplant.

Infants listed for transplantation may be considered for an ABO-incompatible heart transplant based on their antibody levels and age. The United Network of Organ Sharing (UNOS) protocol is infants under 24 months with titers less than or equal to 1:4.1

This recipient’s anti-A and anti-B antibodies were monitored with titer assays to determine their levels; antibody levels less than 1:4 are acceptable pre-transplant in order to proceed with donor and transplant arrangements.1 Immediately prior to initiating cardiopulmonary bypass (CPB), a complete whole body exchange transfusion of at least two-times the patient’s circulating blood volume was performed with packed red blood cells (pRBC), fresh frozen plasma (FFP) and 25% albumin. Titer assays were sent two minutes after initiation of full CPB and then hourly until the cross-clamp was removed. Institutionally, reperfusion of the donor heart is not restored until the antibody level from the titer assay is known and reported as less than 1:4; failing to achieve an immunologically tolerant recipient will provide conditions for hyperacute rejection. The blood collected during the transfusion exchange was immediately processed through a cell saver so the pRBC’s could be re-infused to the patient during CPB, as necessary. The remainder of the transplant was performed in the same fashion as an ABO-compatible heart transplant. The patient has shown no signs of rejection following transplantation.

Keywords
ABO-incompatible; pediatric; perfusion; transplantation; heart

Introduction
Heart transplants have been utilized as the gold standard of the treatment for end-stage heart failure. In January 1996, the first pediatric ABO-incompatible heart transplant was performed in Toronto, Canada at the Hospital for Sick Children on a 25-day-old patient with hypoplastic left heart syndrome (HLHS). The transplant was reported to be successful, with no noted complications or other required heart transplants.1-5

The mortality rate on the pediatric waiting list for heart transplantations was 58% before 1996 in Toronto. The high mortality rate was attributed to the limited supply of donor hearts along with them being both size- and ABO-compatible for a recipient. After the institution of ABO-incompatible organ transplantation, mortality on the waiting list for hearts declined to 7-10%.2-5 ABO-incompatible organ transplantations are possible with infants due to their immature immune system which tends to not produce isohemagglutinins until age 12-14 months.2-4,6

During the fetal stages of life, as early as 20 weeks of gestation, an infant’s immunoglobulin production is

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suppressed. The maternal immunoglobulins (IgG) enter the fetal circulation by crossing the placenta. Natural suppressor cells delay T lymphocyte activation for a period of time following birth. Once active, they lead to B cell activation to produce immunoglobulins. At age 6-8 months, actual development of isohemagglutinins begins to appear after gut colonization with *Escherichia coli* (E. coli). Monitoring for anti-A or anti-B antibody (isohemagglutinins) is crucial in determining whether the transplant will be successfully accepted or immediately rejected. Sudden intravascular activation of the complement system occurs when blood group antigens on the endothelial cells of the donor organ react with recipient antibodies. When activation of the complement clotting cascade occurs, hyperacute rejection ensues, causing immediate destruction. Therefore, careful selection of blood products, such as packed red blood cells (pRBCs), fresh frozen plasma (FFP), platelets and cryo-precipitate (cryo), need to be made based on the recipient and donor blood types.

Patients listed for ABO-incompatible heart transplants with the United Network for Organ Sharing (UNOS) are required to have titer assays run when placed on the transplant list and then monthly until a heart becomes available. Once a heart is available, a titer test needs to be run immediately in order to proceed with donor arrangements. UNOS policy states that, with infants less than 24 months with a titer assay result of 1:4 or less, it is acceptable to proceed with transplantation.1 Once a heart is available, a titer is placed on the transplant list and then monthly until a plant will be successfully accepted or immediately rejected. Sudden intravascular activation of the complement system occurs when blood group antigens on the endothelial cells of the donor organ react with recipient antibodies. When activation of the complement clotting cascade occurs, hyperacute rejection ensues, causing immediate destruction. Therefore, careful selection of blood products, such as packed red blood cells (pRBCs), fresh frozen plasma (FFP), platelets and cryo-precipitate (cryo), need to be made based on the recipient and donor blood types.

Intra-operatively, titer assays need to be sent after a complete blood transfusion and then hourly until the cross-clamp is removed. Institutionally, titer assays that are 1:4 and below are acceptable for proceeding without further transfusions.

Before initiating cardiopulmonary bypass, the patient received a complete blood exchange transfusion. The bypass circuit was primed with recipient-compatible pRBCs along with recipient/donor-compatible FFP. During the complete exchange transfusion, one and half to two times the patient's original blood volume was collected while compatible blood products were transfused to the patient with the cardiopulmonary bypass (CPB) machine. Following the exchange, a cell saver device was utilized to wash the RBCs and remove all of the plasma and white blood cell (WBC) components. The pRBCs salvaged during the exchange were safe to be re-administered to the patient. A complete exchange transfusion was utilized to remove the majority, if not all, of any anti-A or anti-B antibodies that the recipient may have produced. Titer assays determine the effectiveness of the complete exchange transfusion. If the titer assays had come back positive or greater than 1:4 for antibodies, the process of exchange transfusion would have needed to be repeated before the removal of the cross-clamp.

## Case Report

The patient was a one-month-old baby girl (58 cm, 3.83 kg). She was delivered via an emergent cesarean section at 36.1 weeks. In utero, she was diagnosed with dilated cardiomyopathy. There is a family history of dilated cardiomyopathy; the patient's father received two successful ABO-compatible heart transplants due to his dilated cardiomyopathy. The patient was also diagnosed with hyperbilirubinemia at birth. Ten days after birth, the patient was listed on UNOS as status 1A due to her cardiomyopathy under ABO-incompatible since her blood type is O positive. Anticipating a long transplant wait, she was worked up for a Berlin Heart EXCOR® ventricular assist device (VAD) implantation. Fortunately, an ABO-incompatible heart, from a blood type B donor, became available before implantation of the VAD was required. The patient's titers on the day of transplantation were 1:1 for both anti-A and anti-B antibodies.

The perfusion materials were comprised of the Terumo® Advanced Perfusion System I with TLink™ Data Management System for the console. The Terumo® Capiox® FX05 oxygenator with an Integrated Arterial Line Filter and the Terumo® Capiox® Cardiotomy Reservoir (all Terumo Medical Corporation, Ann Arbor, MI, USA). The cannulas utilized were the Edwards® Lifesciences™ 8 Fr. Fem Flex II femoral arterial cannula and two Edwards® DLP Metal Tip 12 Fr. venous cannulas (Edwards Lifesciences Corp., Irvine, CA, USA).

The pump prime contained 1550 mL of PlasmaLyte A, 25 gm of 25% albumin, three units of O negative red blood cells, 316 mL of AB positive fresh frozen plasma. Nineteen and fifty milliliters of PlasmaLyte A was utilized initially to prime the CPB circuit. After three units of pRBC and one unit of FFP were added to the prime, the prime was hemoconcentrated. Eleven hundred and fifty milliliters of ultrafiltrate was removed during hemoconcentration. A blood gas of the prime was run after ultrafiltration. Based on the blood gas, an additional 600 mL of PlasmaLyte A was added to the circuit to allow for further ultrafiltration of 350 mL. A total of 1500 mL of ultrafiltrate was removed before bypass, known as pre-bypass ultrafiltration (pre-BUF). Sixty milliliters of pump prime was removed after pre-BUF for anesthesia to utilize if needed before bypass. Prime medications included: 50 mEq of sodium bicarbonate, 1.9 gm 20% Osmotrol (0.5 gm/kg), 7000 units of heparin and 500 mg of calcium chloride (at the initiation of bypass).

Additional precautions and actions need to be considered prior to full initiation of bypass when performing a complete blood transfusion exchange. Pump suckers are not allowed to be turned on until full initiation of bypass is achieved in order to provide as successful as possible exchange. Otherwise, the patient's current
blood, with its level of isohemagglutinins, would be mixed with the low levels of isohemagglutin in prime components and could affect the integrity of the exchange. Second, both caval cannulas should be in place prior to the transfusion exchange in order to optimize the process and ensure that the majority of the patient's blood is removed. Third, the patient's blood that was fully heparinized and contained antibiotics is completely removed to a collection device. Therefore, the full dose of heparin needs to be included in the prime components and antibiotics need to be re-dosed immediately following the transfusion exchange.

A sterile collection reservoir, such as a cell saver reservoir, is utilized to collect the two times the patient's calculated blood volume during the complete blood exchange transfusion. Utilization of a sterile collection reservoir allows for processing the patient's blood volume in a cell saver device. A “Y” connector is spliced into the venous line in order to incorporate the collection reservoir into the circuit to allow for easy collection of the patient's original blood volume during the complete blood exchange transfusion. Before initiating bypass, the venous line was clamped to both the hard-shell venous reservoir (HSV R) and the collection reservoir. Upon initiation of the exchange transfusion, the clamp to the collection reservoir was removed to allow the patient's blood to be collected in the cell saver reservoir, while the line to the venous reservoir remained clamped. Two times the patient's calculated blood volume was sequestered in the cell saver reservoir before removing the clamp to the HSV R and placing it on the line to the collection reservoir. This would be considered as initiation of full bypass, following a complete blood transfusion. Collection of the patient's blood usually takes 60-90 seconds. Marking a line on the collection reservoir allows for easy visual verification of a complete removal of two times the patient's blood volume. Following the exchange transfusion, the patient no longer had circulating platelets and had limited clotting factors. Therefore, anesthesia was prepared post-bypass with platelets, plasma and cryo. These products needed to be given immediately following protamine administration.

During the complete exchange transfusion, the perfusionist removed 750 mL of volume in a cell saver reservoir before complete initiation of bypass. The volume was processed in a cell saver; 180 mL of volume was returned to the patient from the cell saver while on bypass. Titer s were sent two minutes after full initiation of bypass following an exchange transfusion and again an hour later before the cross-clamp was removed. The titers returned as 1:2 both times for anti-A antibodies and 1:0 followed by 1:1 for anti-B antibodies.

The patient was cooled to 32°C during implantation of the donor heart. Before the cross-clamp was removed, a bolus of 50 mg of methylprednisolone was administered in the pump. Upon re-warming and removal of the cross-clamp, the patient received 130 mL of FFP and another 1.9 gm of 20% Osmi tol. The donor heart cross-clamp time was 178 minutes, the recipient's cross-clamp time was 68 minutes and the pump run was 178 minutes. Modified ultrafiltration was performed for 6 minutes post-bypass, which removed 250 mL of ultrafiltrate. The patient received an additional 400 mL of RBC from anesthesia, which was processed by the cell saver after bypass.

Upon closing the sternum, there was an increase in filling pressures from 12 to 16 mmHg, with a decrease in tidal volumes and a saturation of 90%. The decision was made to delay sternal closure in order to avoid compression to the heart and lungs. The sternum was successfully closed on post-op day 3.

For immunosuppression, the patient was started on mycophenolate mofetil and methylprednisolone post-op followed by intravenous immunoglobulins (IVIG). Three doses of thymoglobulin were administered within the first 8 days post-transplant. Tacrolimus was started 48 hours post-transplant and adjusted, as needed, by the transplant team. Our institutional immunosuppression regimen is a thymoglobulin dose of 1-2 mg/kg/day x 5 doses, IV methylprednisolone, mycophenolate mofetil started immediately following surgery to a targeted level of 2-4 and tacrolimus started 48-72 hours following surgery to a targeted level of 10-13.

The weekly echocardiographs showed normal biventricular function post-transplant. The course to full recovery was somewhat complicated due to post-transplant hypertension along with continued conjugated hyperbilirubinemia. The patient was discharged 40 days post-transplant and has remained stable and healthy at her weekly check-ups.

Discussion

Overall survival rates for pediatric heart transplants are 70% at 4 years post-transplant and, at 10 years, declines to 55%. For pediatric heart transplants, the highest group at risk is infants who are less than a year old. They have a 40% mortality rate within 30 days post-transplant. Of those able to survive their first year after transplant, they have a 90% survival rate at 4 years. Based on Patel et al., 30-day mortality rates for ABO-incompatible were 5.9% compared to 8.8% for ABO-compatible heart transplants. At one year post-transplant, the mortality rate for ABO-incompatible was 14.7% and 16.6% for ABO-compatible. The Kaplan-Meier estimate between 1999 and 2007 for ABO-incompatible and ABO-compatible heart transplant survival rates both approached 70% at 3 years post-transplant. 6

West et al. compared rejection patterns among recipients of ABO-compatible and ABO-incompatible heart transplants. None of the patients experienced hyperacute rejection. In the ABO-incompatible group, six patients
suffered from a single occurrence of acute cellular rejection, less than or equal to six months post-transplant. The episodes were short-term and resolved with high-dose glucocorticoid therapy. In the ABO-compatible group, seven patients suffered from multiple occurrences of acute cellular rejection. Each patient suffered at least one rejection, less than or equal to six months post-transplant, then again greater than six months post-transplant. The incidence of rejection episodes in ABO-compatible heart transplants were slightly more frequent than in the ABO-incompatible heart transplant patients. The increased incidence of rejection may be attributed to the differences in immunosuppression therapy following transplant. The ABO-incompatible patients tend to receive a more rigid combination of tacrolimus with mycophenolate mofetil.3

Thirty-five ABO-incompatible heart transplants were performed within the United States from 1999-2006. Compared to the total number of infants transplanted during this period, they comprised 6% regardless of the infant waiting-list mortality of 25-50%.4,5 Toronto’s infant mortality rate has remained below 15% from 1996-2006 since the utilization of ABO-incompatible heart transplants. With this data, why is ABO-incompatible heart transplantation not a more embraced universal practice?5

Irving et al. compared median wait times for infants listed for ABO-incompatible and ABO-compatible heart transplants. They found that the wait time for ABO-incompatible tends to be two weeks less than for those waiting for an ABO-compatible heart transplant. Other comparisons show similar results, with waiting times of 72 days and 54 days for ABO-compatible and ABO-incompatible heart transplants, respectively. Unfortunately, the United States currently utilizes the ABO-incompatible waiting-list primarily for sicker children instead of using it to its full potential.4

There is controversy over the maximum age limit for ABO-incompatible heart transplants. As stated previously, UNOS’ policy is infants under 24 months with a titer assay less than or equal to six months post-transplant. The age limit should be and the titer assay range for successful transplantations. There are a lot of factors that play into it, such as pre-transplant blood transfusion and extracorporeal membrane oxygenation (ECMO) requirements.6

ABO-incompatible heart transplants defy the logic of successful transplantations. ABO-incompatible heart transplants are successful and possible with the development of policies and procedures through collaboration of a multi-disciplinary team approach. Comparing survival and rejection rates among ABO-compatible and ABO-incompatible heart transplant recipients, their outcomes are equivalent.3,6 Median transplant waiting-list times are shorter for ABO-incompatible versus ABO-compatible,4 which, in turn, helps decrease infant waiting-list mortality rates.5 The next step is to define the age limit and titer assay range for successful transplantation with ABO-incompatible donor organs. The full potential for utilizing ABO-incompatible heart transplants is still to come.

Declaration of Conflicting Interest
The authors declare that there is no conflict of interest.

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