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From Incompatibility to Accommodation – The Journey of Taming 'Self': Guide to Perioperative Management of Solid Organ Transplantation across ABO and Rh Barrier

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Abstract

The fate of every organ allografting is 'rejection' if nothing is done to halt this natural process. The risks of 'hyperacute' 'accelerated acute' and 'acute' rejection have restricted scientists and clinicians over the years in performing organ transplantation within ABO blood group matched pairs only. Subsequent to the development in the field of immunosuppression, ABO incompatible transplants have gained momentum to incorporate a significant population of end stage renal disease patients with incompatible blood group donors into the transplant program. However, optimizing the recipient for transplantation and subsequent accommodation with optimal graft function without tilting to the much easier path of rejection is a challenge. Although most of these steps come under the domain of the nephrologist, it is crucial that as the perioperative physician of a very high stake life modifying surgery, the anesthesiologist, surgeons as well as the intensivist should understand the complex process of desensitization, patient preparation and perioperative management for the best outcome. Lack of understanding about a couple of crucial considerations can jeopardize the delicate balance of immunotolerance and can prove catastrophic. The article highlights these considerations important for the perioperative clinicians along with a description of first 20 patients of blood group incompatible renal transplantation at our Institute.

Keywords: Organ transplantation; ABO incompatible; Rh incompatible; Plasma exchange; Double filtration; HLA matching; Antibody mediated rejection; Immunosuppression; Accommodation; Blood products; Coagulopathy

Introduction

"We do not feel that renal transplantation in the presence of blood incompatibility is wise". - Humes et al.

The pioneers in the field of ABO incompatible (ABOi) renal transplantation, Humes and colleagues lost their two initial patients in the year 1951 within a month of surgery [1]. Wordwide, the waiting list of prospective kidney transplant patients have gone up exponentially. United states 2013 data shows on an average 36000 patients are added in the kidney transplant waiting list which in itself has more than 1 lakh entries. Of these only 16,800 odd patients were operated upon in the year 2013 [2]. Such dismal scenario is mainly because of the lesser acceptance of the living donor renal allografting program in some countries and lack of blood group matched donors. The fear of ,graft rejection' and increasing the morbidity of recipient were the reasons behind the selective avoidance of transplant pairs with blood group incompatibility. Subsequently, with better understanding and developments in the field of immunology and immunosuppressive agents, improvised and selective techniques of antibody removal, combined with some landmark case series especially from Japan, today ABOi transplants have comparable outcome in terms of long term graft survival with that of compatible ones [3]. In tune with the rest of the world, ABOi renal transplantation program was started at our institute in November 2013.

The ABO system and their surface antigenicity

The ABO blood group antigens are oligosaccharide surface antigens expressed on red blood cells, vascular endothelium, renal tubules and other body tissues and body fluids [4,5]. Universal to all the blood group antigens and the sole antigen in blood group ,O' is the H antigen [3]. Addition of specific carbohydrate determinants to the H-antigen finally determines the blood group. Moreover, the density of A-, B- or O (H) antigen expression differentiates the various subgroups of ABO system which has a significant impact on antigenicity in transplant immunology. For example A1 subgroup has higher antigen expression than A2 or A3 [6] and B have lesser antigenic expression than A1 [7]. It is believed that antibodies against the other blood group types develop after birth in response to carbohydrate antigens expressed by bacteria that normally colonize the bowel [3]. With the exception of blood group 'O' as 'universal donor' and blood group 'AB' as ,universal 'recipient', any other non matched group transplantation carries the risk of antibody mediated rejection (ABMR) if the group specific antibodies are not removed from the recipient's blood beforehand.

Preformed antibodies and antibody mediated rejection

Hyper acute rejection is a possibility despite adequate cross matching and optimal pre transplant removal of anti-ABO natural antibodies [8]. In addition, acute rejection can develop during the first few weeks after ABOi transplantation via antibody-mediated humoral response. Antibody mediated rejection (ABMR) can be diagnosed based on clinical, immunologic, histopathological and serological evidences (Table 1).

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Preparing the donor

ABOi transplantations have significant financial implications costing around 72% more than the conventional ABO compatible transplants. But still it is considered to be less expensive than maintaining renal replacement by dialysis [9]. Inspite of such a high cost intervention, the chances of antibody mediated rejection is higher. The other option that should be explained to both donor and recipient is the 'paired exchange programme', where the donors from two incompatible pairs cross donate their kidneys to compatible contralateral recipients.

Perioperative Considerations

Apart from the routine protocol of preanesthetic workup of transplant patients, special attention should be given to the following concerns:

Isoglutinine titre

The effectiveness of the 'Desensitization' protocol for ABO antibody removal is tested by intermittent measurements of the Isogglutinine level. Two-fold serial dilutions of the patients' serum with commercially available A/B indicator red cells are done to measure the anti-A/B antibody titers. The highest serum dilution ratio that showed 1+ reactivity indicates the anti-A/B antibody titre (Table 2).

The desensitisation protocol

The preparation of the recepient involves 'Desensitization' based primarily on two principles:

1) Removal of preformed antibody by using extracorporeal techniques: Presently three techniques are primarily followed for antibody depletion – therapeutic plasma exchange, double-filtration plasmapheresis, and antigen-specific immunoadsorption. Therapeutic plasma exchange is the simple, cheap and the most commonly used modality of antibody removal. However, it has poor efficacy in terms of plasma volume processed and poor selectivity as it also depletes coagulation factors and antiviral and antibacterial immunoglobulins [10]. Double-filtration plasmapheresis and antigen-specific immunoadsorption are selective techniques of antibody removal [11]. These extracorporeal techniques of antibody removal are on top of the routine dialysis schedule.

Parameter	Findings
Clinical	Decrease in urine output and rise in creatinine levels
Immunologic	• C4d deposition in the peritubular capillary • Presence of immunoglobulin and/or complement in fibrinoid necrosis
Histopathological	• Peritubular capillary and /or glomerular leucocyte infiltration • Glomerular and arterial thrombi with arterial fibrinoid necrosis • Acute tubular injury
Serological	Circulating antidonor antibodies

Table 1: Clinical, immunologic, histopathological and serological evidences.

Donor Blood Group	Recipient Blood Group	Testing Performed (Igm And Igg)
AB	O	Anti A, Anti B
B	O	Anti B
A	O	Anti A
AB	B	Anti A
A	B	Anti A
AB	A	Anti B
B	A	Anti B

Table 2: Testing performed for antibody levels as per blood group incompatibility.

2) Inhibition of ongoing Ab production: by splenectomy and use of immunosuppressive drugs.

Splenectomy was previously thought to be an important modality to specifically and irreversibly deplete memory B cells, thereby reducing antibody producing B lymphocytes but has lately come under the scanner. A growing body of evidence disapprove splenectomy in ABOi recepients [12] and in turn prefer anti-CD20 monoclonal antibody (Rituximab) induction. Rituximab inhibits B-cell proliferation and induces cellular apoptosis (chemical splenectomy). It has its effects on Pre B, B and Memory B cells (precursor of plasma cells which contribute to Ab production). However, a significant concomitant reduction in immunoglobulin level can render these patients susceptible to infection and wound related complications.

Preoperative use of intravenous immunoglobulin: Helps in downregulation of the antibody mediated immune response. Immunoglobulin administration generally follows every session of plasmapheresis.

A typical desensitization scheme is depicted in Figure 1 below.

Other immunosuppressives: Similar to ABO compatible transplant, 'Triple immunosuppression' consists of Calcineurin inhibitors (cyclosporine and tacrolimus), antimetabolites (mycophenolate mofetil and azathioprine) and low-dose steroids. A fourth agent is frequently used in the form of monoclonal or polyclonal antibody agents (anti-CD25 antibody or antithymocyte globulin) during the induction period. It is important to ensure that the recipient takes all the immunosuppressants on time, especially the preoperative dosage. Knowledge of the immunosuppressant protocol and especially precautions associated with the intraoperative use of interleukin 2 antagonist or antithymocytic globulin is important for their safe administration.

Time of last session of extracorporeal antibody removal technique

Knowledge of the last session of both extracorporeal antibody removal technique and dialysis are important along with the post dialysis fresh blood reports and pre transplant isogglutinine titres. Every institute has their own target for pre transplant isogglutinine titre. In our institute, we aim for a target of ≤ 1:8. Some patients may show a significant rebound increase in isoagglutinine titers despite multiple sessions of plasmapheresis preoperatively. These so called 'immunologic high responders' [4,13] are poor candidates for ABO-incompatible transplantation. As already described extracorporeal techniques of antibody removal (except immuneadsorbtion) have the disadvantage of concomitant removal of protective coagulation factors and antibodies making the patient vulnerable to bleeding diathesis and infections [10]. The maintenance of high level of antiseptic precautions throughout, adequate arrangement of blood products, meticulous surgical haemostasis are of utmost importance as the intraoperative blood loss may be higher compared to non-plasma exchange patients.

Immunosuppressive effects of stress response and anesthesia

ABO-incompatible transplantation requires more intense and costly immunosuppressive therapy [14-16]. Moreover, perioperative anxiety and stress response are potentially immunosuppressive. It is important to understand that such immunosuppression can jeopardize

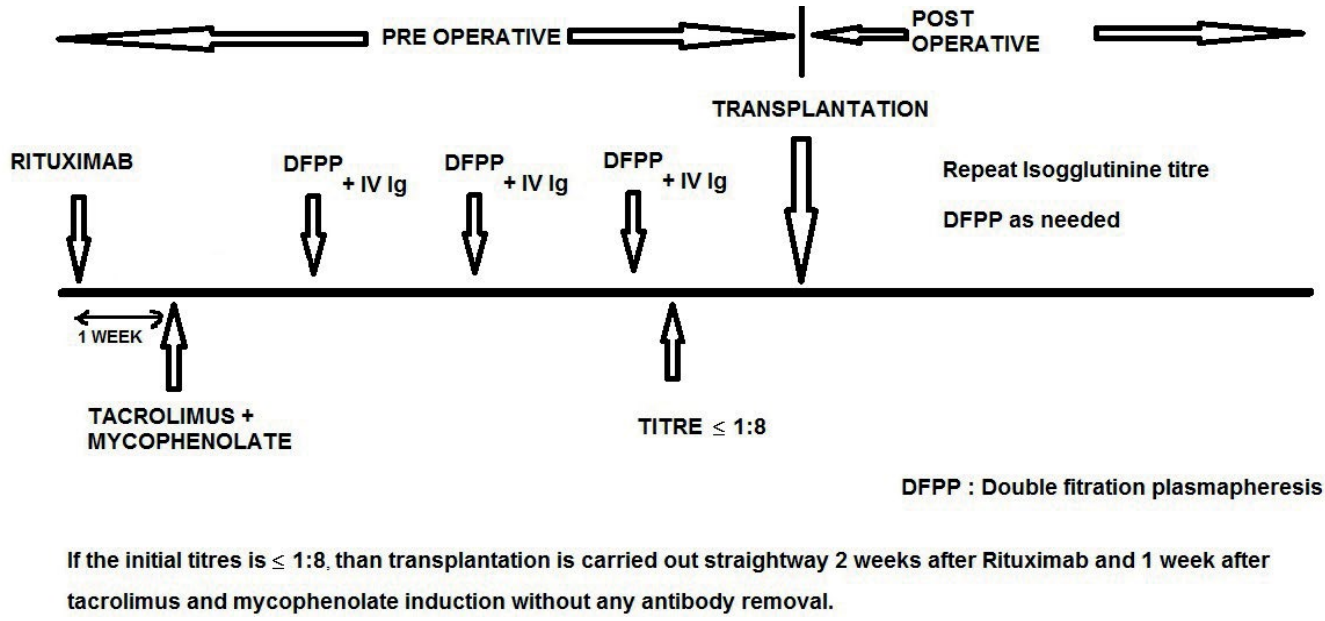

Figure 1: Antibody removal and desensitisation protocol follwed at our institution.DFPP: Double Filtration Plasmapheresis; IVIg: Intravenous Immunoglobulin.

the already maximally suppressed B and T cell immunity in transplant recipients and therefore is undesirable. To maintain homeostasis every effort should be made to reduce the immunomodulating influence of perioperative stress. Preoperative anxiolysis, smooth conduct of anesthesia and regional block techniques, use of potentially immunostimulating regional analgesia and avoidance of conditions known to reduce immunity (eg: high dose opioids, postoperative pain, hypothermia) are some of the steps towards that goal.

Perioperative blood product transfusion

Blood products should be arranged as per the compatibility profile as depicted in the table below (Table 3).

Use of a blood product not tallying with the above list can induce severe antigen antibody reaction and seriously effect the graft outcome.

Postoperative Considerations

A lowered threshold for rejection alarm, repeat follow up of isogglutinine titre, safe use of blood products, strict asepsis are some of the considerations which should be strictly followed over and above the usual issues of a routine ABO compatible transplant. In our institution we repeat the antibody titre on the 1st post operative day. If the measurement is within recommended range of 1: 8 and the graft is functioning well, then the titre is repeated daily for 1 week. Thereafter, titres are measured twice weekly for two weeks and plasmapheresis is done in case there is persistent rise in antibody titre.

In a transplant patient adequate post operative pain relief is of utmost importance to break the cycle of pain induced sympathetic over activity and the subsequent vasoconstriction of the graft vessels. However, in an ABOi recipient prepared by plasmapheresis, the possibility of coexisting coagulopathy should be kept in mind and the safety of insertion of a catheter for central neuraxial regional analgesia should be evaluated on a case to case basis. Other modalities of post-operative pain relief like intravenous opioid by infusion or patient controlled analgesia are good options.

Considerations in a Rh incompatible transplantation

Two main considerations during Rh incompatible (Rh positive donor and Rh negative recipient) transplantation are: blood product management and RhIG prophylaxis especially in a female patient. Packed RBC should be Rh-compatible with the recipient's blood type and platelet concentrate, fresh frozen plasma and cryoprecipitate should be Rh-compatible with the donor [17]. This can sometimes be a limiting factor in prior arrangement of blood products for a rare blood and Rh group patient. Although an immunosuppressed patient is less likely to mount an effective response to RhD antigen, still prophylactic RhIG can be considered in case of Rh^+ RBC transfusion especially in female patients (of any age) who may get future exposure or might have been previously exposed to Rh^+ RBCs (via transfusion or pregnancy) prior to the free availability and protocolisation of perinatal Rh immune globulins.

The process of accomodation

Once the acute postoperative phase is over, anti donor blood group antibodies start rising in the recipient despite the use of immunosuppressive agents. But, even then the graft continues to function normally and exhibits apparent resistance to humoral rejection even in the presence of antibodies directed against the graft endothelium [18]. This phenomenon is called ,accommodation' [19,20]. This is because of the long term natural protection that makes ABOi transplants a possibility. Although precisely not known, various theories have been postulated for the mechanism of accommodation:

- An active change in endothelial cell physiology or phenotype
- Expression of "protective gene" products that render the graft resistant to the effects of complement and other activating stimuli [21,22]
- Inhibition of inflammation by complement split products like iC3b and C3a

Recipient	Donor	PRBC	FFP 1st choice	FFP 2nd choice	Platelets 1st choice	Platelets 2nd choice	Remarks
O	A	O	AB	A	A	AB	• First choice FFP is of AB group. • PRBC is of either recipient's own blood group or O group
O	B	O	AB	B	B	AB	
O	AB	O	AB	A	AB	A	
A	B	A or O	AB	A	AB	B	
A	AB	A or O	AB	A	AB	A	
B	A	B or O	AB	B	AB	A	
B	AB	B or O	AB	B	AB	B	

Table 3: Recommended use of blood products in ABOi transplantation. PRBC: Packed Red Blood Cell; FFP: Fresh Frozen Plasma.

- Up regulation of various cytoprotective mechanisms by endothelial cells
- Disruption of normal signal transduction
- Attenuation of cellular adhesion
- Prevention of apoptosis

ABOi Organ Transplantation in Children

Long term data so far have suggested that younger recipients (<15 years of age) have excellent outcome following ABOi renal transplantation with 100% graft survival rate at 1 year and 95% at 2 to 9 years [4]. This is probably because of the immaturity of the immune system. Reported infectious complications are also few in the pediatric population [15,23]. However, post-transplant, viral infections (Cytomegalo virus, *Pneumocystis carinii*, *Listeria monocytogenes*, and *Aspergillus fumigatus)* are common [24]. The risk of primary cytomegalo virus (CMV) infection in children following transmission from a CMV-positive donor warrants appropriate prophylaxis (antiviral chemotherapy) preoperatively [25,26].

Conclusion

Increasing numbers of case series and evidences show that ABOi kidney transplantation is a feasible option and more and more centers are inculcating it into their transplantation program. Although newer age immunosuppressants and antibody removal techniques have made it possible, still transplantation across ABO barrier should be considered as 'high risk' in terms of graft acceptance and function. Needless to say it demands multispecialty involvement and thorough understanding of the topic. But unfortunately, not much information and scientific data are available addressing the perioperative management concerns of such patients especially catering to the requirements of non nephrologists who otherwise play significant role in the transplantation program. We think our article will help in adding some information in this field.

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