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ABO incompatible renal transplant: Transfusion medicine perspective

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Abstract:

INTRODUCTION: Our study presents an analysis of the trends of ABO antibody titers and the TPE (Therapeutic Plasma Exchange) procedures required pre and post ABO incompatible renal transplant.

MATERIALS AND METHODS: Twenty nine patients underwent ABO incompatible renal transplant during the study period.The ABO antibody titers were done using the tube technique and titer reported was the dilution at which 1+ reaction was observed. The baseline titers of anti-A and anti-B antibodies were determined. The titer targeted was ≤8. Patients were subjected to 1 plasma volume exchange with 5% albumin and 2 units of AB group FFP (Fresh Frozen Plasma) in each sitting. TPE procedures post-transplant were decided on the basis of rising antibody titer with/ without graft dysfunction.

RESULTS: The average number of TPE procedures required was 4-5 procedures/patient in the pretransplant and 2-3/patient in the post-transplant period. An average titer reduction of 1 serial dilution/procedure was noted for Anti-A and 1.1/procedure for Anti-B. Number of procedures required to reach the target titer was not significantly different for Anti-A and Anti-B ($P = 0.98$). Outcome of the transplant did not differ significantly by reducing titers to a level less than 8 ($P = 0.32$). The difference in the Anti-A and Anti-B titers at 14th day post-transplant was found to be clinically significant ($P = 0.042$).

CONCLUSION: With an average of 4-5 TPE procedures pretransplant and 2-3 TPE procedures post transplants, ABO incompatible renal transplantations can be successfully accomplished.

Key words:

ABO incompatible, renal, therapeutic plasma exchange, titer

Renal transplant remains the best treatment option for end-stage renal disease (ESRD) patients. This not only allows them a better quality of life but also eliminates or reduces the morbidities associated with dialysis. As per the study conducted by Agrawal,[1] the prevalence of ESRD in India is nearly 785 per million populations. They found diabetes as the predominant cause of the disease. With growing burden of diabetes and the increasing proportion of elderly population, chronic kidney disease (CKD) has attended an epidemic status in the country.[1]

The first criterion that is taken into consideration for solid organ transplants is ABO compatibility between donor and recipient, followed by human leukocyte antigen (HLA) matching.[2] Availability of an ABO compatible donor for ESRD patients is a challenge due to several reasons among which CKD in the family members and limited availability of cadaver organs for transplantation are a few.[1] The ABO antigens are expressed on the vascular endothelium, distal convoluted tubule, and collecting ducts in the kidney.[3] The naturally occurring antibodies against the ABO antigens that are absent on the recipients' red cell surface or the tissues are the mediators of antibody-mediated rejection (AMR). An AMR due to ABO antibodies, HLA antibodies, or any alloantibody against a blood group antigen that takes place within minutes to hours of transplant is considered a hyperacute rejection (HAR). This is the most significant obstacle for an ABO incompatible renal transplant.

Renal transplants across ABO blood groups have been made possible by desensitization therapy. It is estimated that an additional 10–20% of living donor kidney transplantations can be performed through the implementation of such programs,[4,5] thereby reducing morbidity and mortality in patients on the waiting list. A 30% increase in availability of organs for transplantation by performing ABO incompatible transplants has

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been quoted.[6] Among the most significant developments in ABO-incompatible, solid-organ transplantation with immediate clinical applicability and impact are the application of plasma exchange and immunoadsorption protocols to reduce recipient isoagglutinin levels before and after transplantation. Here comes the role of a transfusion medicine expert who conducts the ABO titration, actively reports it to the concerned physician, plans for the therapeutic plasma exchanges (TPEs), and executes it. The role continues after the transplant at least till the accommodation sets in. Furthermore, the transfusion medicine expert has to attend to any adverse outcome of the graft in the form of AMR for which TPE is a modality of treatment.

We present an in-depth analysis of the ABO titers and the TPE procedures required to ensure better results in cases of ABO incompatible renal transplantation conducted in our institution

Materials and Methods

The data were compiled by the Department of Transfusion Medicine, Indraprastha Apollo Hospitals, New Delhi, prospectively from June 2012 to August 2015. The Institutional Ethical Committee approval was taken. During this period, 29 patients underwent ABO incompatible renal transplant at our center. ABO antibody titers and TPE for titer reduction were done at our department. All patients were evaluated for complement-dependent cytotoxicity NIH antihuman globulin (AHG)-augmented HLA cross-match to detect donor specific IgG antibodies to Class I and Class II. The blood group of the donors and the recipients was determined by the fully automated immunohematology analyzer Neo/Galileo (Immucor, INC Norcross, GA, USA). All the 29 patients were screened for atypical antibodies against the red cells before the transplant and all of them were negative. All relevant clinical and laboratory data were recorded from the patients' case files and the patients were followed up until discharge from the hospital.

The ABO antibody titers were done using the tube technique at polyspecific AHG phase. The titers of anti-A and anti-B antibodies were determined before the initiation of any immunosuppressive therapy. This was termed the "baseline titer." An IgG titer of ≤8 was considered acceptable for the transplant. The titers mentioned in the text hereafter will be referring to the titer of the target antibody, i.e., the antibody against which the incompatibility is present.

In our center, plasma exchange was done using the Haemonetics MCS + cell separator (Braintree, MA, USA) using kit REF 981E (Braintree, MA, USA). Exchange of 1 plasma volume was done for all the patients. The replacement fluid used was 5% albumin solution with 2 units of fresh frozen plasma (FFP) of AB blood group toward the end of the plasma exchange procedure each time. The same proportion of fluids was used posttransplant unless otherwise indicated. The patient who had thrombotic microangiopathy (TMA) following transplant, the replacement fluid used was exclusively FFP of group AB. The anticoagulant used was ACD-A in all the procedures of TPE. A ratio of 16:1 of whole blood to ACD-A was maintained throughout the procedures. Calcium gluconate 10% diluted in 100 ml of 0.9% normal saline was prophylactically used each time as a continuous intravenous drip through a peripheral line. The minimum dose used was 2 ampoules of 10 ml each for an exchange volume of 3–4 L. Further increase in dose depended on the symptoms and signs of citrate toxicity if any.

The desensitization protocol followed was rituximab (375 mg/m^2) administered at the beginning of the therapy (10–12 days prior to the transplant) along with the immunosuppressive drugs, comprising tacrolimus (dose = 0.10–0.12 mg/kg), mycophenolate mofetil (dose = 1 g twice a day), and steroids in appropriate doses, followed by TPE. The serum level of tacrolimus targeted was 5–8 ng/ml.

The TPE procedures were done on daily basis, and intravenous immunoglobulin (IVIG) (dose = 100 mg/kg) was given immediately following the TPE procedure. Antibody titers were repeated every day. The number of TPE procedures depended on the baseline titer; higher the titer more the number of TPEs required and were continued till the desired titer of ≤8 was reached.

Following transplant, further TPE procedures were done in case of rising antibody titers (beyond 8) with or without graft dysfunction or in case of derangement of the renal profile in the form of increasing creatinine and/or decreased urine output. Posttransplant TPE was also performed in patients who developed complications such as TMA where TPE is one of the preferred treatments.

The patients were observed during their hospital stay which ranged from 14 to 55 days. The ABO antibody titers were assessed on daily basis for 14 days. The titers guided the performance of further TPE procedures.

Any complication during the postoperative period was recorded. AMR was assessed on the basis of renal parameters and kidney biopsy. Kidney biopsies were performed only on the patients who had features of graft dysfunction, viz., a decrease in urine output and/or an elevation of serum creatinine. Details of any postoperative TPE procedure done for treating AMR were also recorded. Short-term patient outcome was assessed based on graft function.

Statistical analysis

For the purpose of statistical analysis, the patients were divided into two groups on the basis of outcomes, i.e., favorable and unfavorable. Any graft dysfunction, HAR, or any other complication as a consequence of the ABO incompatible renal transplant was included in the unfavorable group. Data were entered in the Microsoft Excel (Redmond, WA, USA), and SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA) was used for analysis. To find out the association between qualitative or grouped data, Chi-square test/Fisher exact test was used as and when required. Mann–Whitney U-test was used to test the significance of response of different variables (pretransplant TPE, posttransplant TPE, etc.) for two groups defined by relative antibody status of patients. For all statistical tests, a $P < 0.05$ is considered statistically significant.

Results

A total of 29 patients underwent ABO incompatible renal transplant during the observation period. This included

7 (24.1%) females and 22 (75.9%) males. The age ranged from 17 to 75 years, with the mean age being 38.7 years. The blood group incompatibilities between the donor and recipient are shown in Table 1.

Table 1: Distribution of ABO incompatibilities among the donors and recipients on the basis of outcomes

Incompatibility involved	Favorable outcome	Unfavorable outcome	Total
B to O	5	2	7
A to B	5	1	6
B to A	3	1	4
A to O	5	1	6
AB to A	3	0	3
AB to B	3	0	3
			29

Figures 1 and 2 depict the baseline titers, the titers on the day of transplant, and the 14th posttransplant day titer for the 29 patients. The baseline titers ranged from 16 to 512 (median = 64). Two patients were transplanted at titer of 8, eight patients at a titer of 4, seven at a titer of 2, and twelve at a titer of 1 on the day of transplant (median = 1).

A total of 202 TPE procedures were done for these 29 patients, out of which 139 procedures were done in the pretransplant period (mean = 4.8/patient) and 63 procedures (mean = 2.2/patient) were done after the transplant. Of the 139 procedures done in the pretransplant period, 67 procedures were done on the O blood group recipients (n = 13) and 72 procedures on other blood groups (n = 16). Of the 63 procedures done during the posttransplant period, 15 procedures were done on O blood group recipients and the rest 48 procedures were done on other blood group recipients. Although the

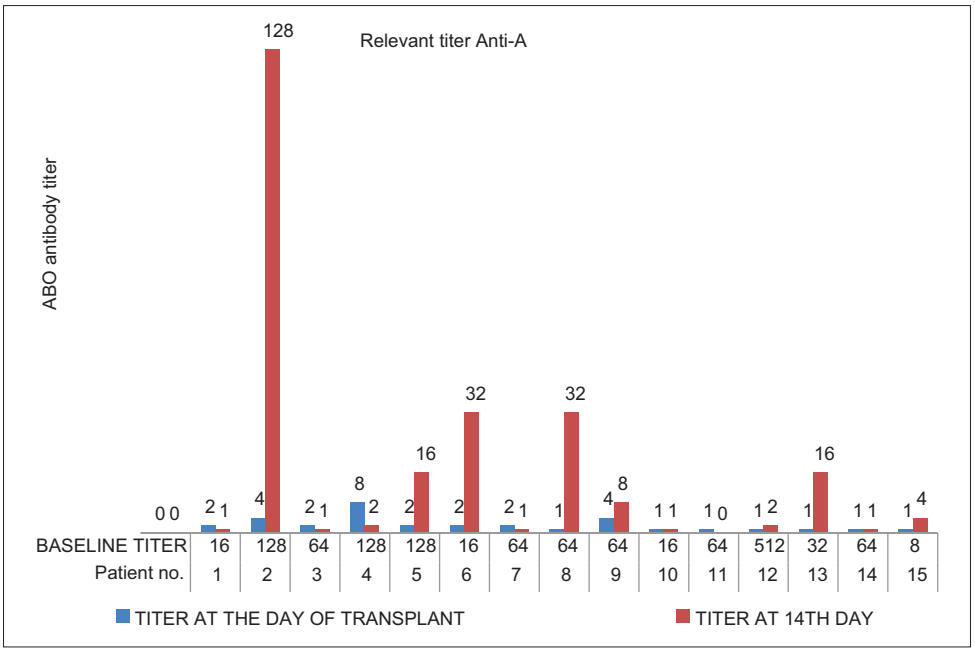

Figure 1: *Baseline titers, titers on the day of the transplant, and titer on the day 14th posttransplant for the patients with relevant titer anti-A*

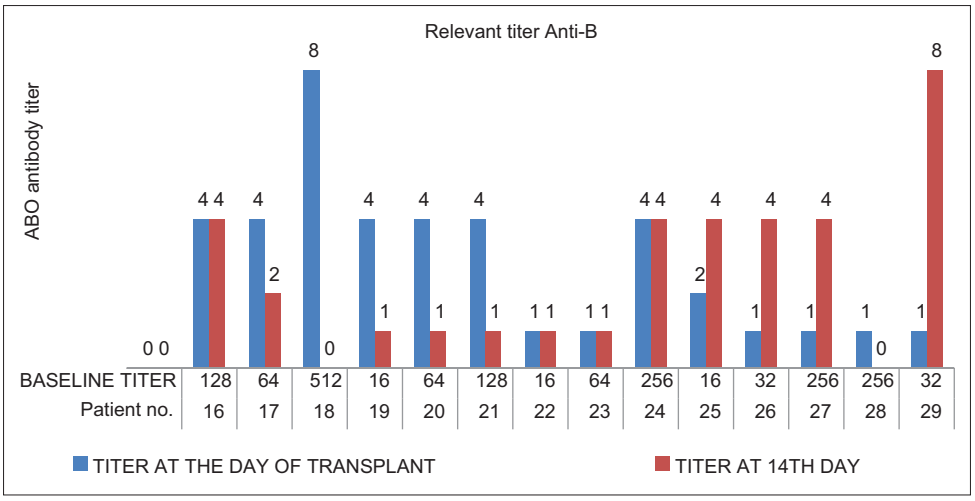

Figure 2: *Baseline titers, titers on the day of the transplant, and titer on the day 14th posttransplant for the patients with relevant titer anti-B*

average number of TPE procedures performed per patient in the posttransplant period was lower in group O recipients as compared to non-O group recipients, the difference was not statistically significant ($P = 0.22$).

The pattern of fall of the antibody titers from the baseline to the pretransplant titer of 8 or less was not uniform requiring 2–11 TPE procedures. On an average, 4.7 procedures were done to reduce the anti-A titer in the pretransplant period. The titer decreased by 1 serial dilution per TPE procedure. Similarly, an average of 4.8 procedures was done to bring the anti-B antibody titer to the desired level pretransplant, with the titer reduction of 1.1 serial dilutions per TPE procedure. In the posttransplant period, the average number of TPE done was 3.1 and 1.4 for the patients with relevant titer anti-A and anti-B, respectively. The number of procedures done for both the relevant titers had no statistically significant difference with $P = 0.98$ and 0.25 for the pretransplant and the posttransplant periods, respectively.

At the posttransplant day 14th, the ABO titers increased to a level greater than the transplant day titer for 11 patients. Two of these 11 patients had the 14th day titers equal to or higher than the respective baseline titers. The details of the 14th day titers, which ranged from 1 to 128 (median = 1) of the 29 patients, are shown in Figures 1 and 2. Majority of the high 14th day titers were anti-A. The difference in the anti-A and anti-B titers at the 14th day was found to be clinically significant ($P = 0.042$).

Outcomes

The outcomes of the transplant were neither influenced by the age of the recipient ($P = 0.842$) nor influenced by the blood group of the recipient ($P = 1.0$). The number of TPE procedures required pretransplant does not differ significantly with the baseline titers being ≤64 or more ($P = 0.10$). The graft outcomes were not statistically different for patients who had baseline titers ≤256 and >256 ($P = 0.32$). Similarly, there was no difference in the graft functions of patients transplanted at titer 8 and those transplanted at titers <8 ($P = 0.32$). In spite of high titers of ABO antibodies in some patients at the 14th day of transplant, good graft performances were observed, indicating that the accommodation had set in by that time.

Of the 29 patients, 24 showed a good response posttransplant with improvement in the renal parameters and urine output. However, 1 patient faced HAR of the allograft within 24 h of transplant. Graft biopsy was performed on 2 patients (1 biopsy each) who faced graft dysfunction during the 1st week of transplantation. The graft of one patient, whose biopsy revealed neutrophil infiltrates in the glomeruli, peritubular capillaries, tubular injury, and C4d staining of 30%, was salvaged with 5 sittings of TPE procedures coupled with other medications. However, the other patient succumbed due to TMA (diagnosed on the basis of clinical features) related complications in spite of 5 TPE procedures and supportive drugs. The biopsy of this patient described coagulative necrosis and hemorrhage in the cortical tissue, absence of viable glomeruli, patchy interstitial edema, congestion of peritubular capillaries, patchy lymphomononuclear infiltrates, and hyaline casts, suggestive of acute AMR. The first patient who faced HAR was transplanted at titer of 8 while the latter 2 patients who faced AMR were transplanted at titers <8. Two patients succumbed within 2–3 days of transplant due to medical conditions not related to ABO incompatibility.

Discussion

The success of ABO incompatible renal transplantation has made possible for more number of ESRD patients to live a better life posttransplant. Techniques such as plasma exchange and drugs such as IVIG and rituximab to reduce the titer of ABO antibodies have paved the path for better outcomes in ABO incompatible transplants. ABO incompatible renal transplantations are being conducted at many centers all over the world. Each center follows its own desensitization protocols and has reported variable graft survival rates.[4-6]

Various techniques for the reduction of anti-A/B titers are now available, one of which is TPE. They differ in their selectivity of the protein removed. In our study, TPE volume exchanged was 1 plasma volume which is within the range described by Gilcher and Smith[7] in their study. With an exchange of 1 plasma volume 63% of the antibodies of the antibodies, especially IgM are removed.[7] Use of TPE to reduce the titers of anti-A and anti-B is the central feature of desensitization therapy before ABO incompatible renal transplants.[8] According to the American Society for Apheresis guidelines, ABO-incompatible kidney transplantation is classified as Category I, in which plasma exchange is considered the first-line of treatment, either stand-alone or in conjunction with other modes of treatment.[9]

There is a lack of a consensus regarding the absolute pretransplant titer at which ABO incompatible transplantation is less likely to face AMR. As in our institution, Tydén *et al*.[5] aimed to achieve IgG titer of <8 on the day of transplantation whereas Tanabe *et al*.[10] had accepted an upper limit of 32 for IgG and IgM titers. Both studies reported good graft survival rates despite the differences. Wilpert *et al*.[11] used a target titer of 4 for all the patients. We tried to analyze if the target titer <8 could have a better result than transplanting at a titer of 8 and found that there is no statistically significant difference ($P = 0.29$). Our observation indicates that the transplant can be planned once the titer of the relevant antibody reaches 8. It seems to be unnecessary to plan further TPE procedures after this target is achieved as this will not only add to the cost of the transplant but also delay it.

As per our analysis, the anti-A titer reduces by an average of 1 serial dilution per TPE procedure whereas the anti-B by 1.1 serial dilutions per TPE procedures. As per the study conducted by Winters *et al*.,[12] the titers reduced by 1.1 dilutions per plasmapheresis/IVIG session, which ranged from 0.5 to 2.0 dilutions for immediate spin reactivity and 0.3 to 3.3 dilutions for AHG reactivity. However, they did not differentiate between the anti-A and anti-B titers.

One of our patients who had blood group O experienced HAR. The O blood group individuals have the anti-A and anti-B antibodies of IgG type predominantly.[13] The IgG antibodies having a major distribution in the extravascular compartment of circulation has a possibility of movement into the intravascular compartment by the time of transplant and causing antibody-mediated graft rejection. This could have been the possible reason of HAR.

Accommodation is a process in which the recipient of an organ develops an acquired resistance to immune-mediated rejection.[11] It takes nearly 2 weeks for the graft to accommodate in the host body.[14] Kayler *et al*.[15] found that a titer of 8 or less is safe in the posttransplant period. Patients, in whom the titer exceeds 64, may suffer AMR. As per Stegall *et al*.,[16] a titer more than 16 in the 2 weeks following transplant needs titer reduction procedures. However, in contrast, in our analysis, we observed that the rise of posttransplant antibody titer beyond 8 (seen in 4 of our patients) was not associated with graft dysfunction which is similar to what Tobian *et al*.[17] demonstrated in their study. They found that the clinical significance of an increased posttransplant ABO antibody level is variable and that there was no dependable correlation with antibody-mediated rejection. We found a clinically significant difference between the titers of anti-A and anti-B at the 14th day posttransplant ($P = 0.042$). The titers of anti-A were found to rebound more often than the titers of anti-B and rise as high as the baseline titer of the patient or beyond. Interestingly, in spite of higher titers of anti-A than anti-B, no adverse impact was seen on the graft, signifying that the graft had accommodated.

However, conventional plasma exchange is not the only modality of TPE. Several other centers in India are also performing ABO incompatible transplants using different type of apheresis techniques such as cascade plasmapheresis. Jha *et al*.[18] and Tiwari *et al*.[19] have found the use of cascade plasmapheresis cost-effective and efficient in their respective studies. Other techniques include antibody specific immunoadsorption column.

Our study is limited by the small sample size of 29 patients, and a larger data would help in providing more conclusive results. A long-term follow-up could have given a better insight into the outcomes of such programs. We did not include a control arm in the form of ABO-compatible donors, which could have highlighted differences in the outcomes of ABO compatible renal transplants as compared to incompatible renal transplants if any. However, our analysis can pave the pathway for establishment of institutional protocols and guidelines to be followed in future.

Conclusion

ABO incompatible renal transplants are possible in all combinations of blood groups of the donor and recipient and thus can act as savior for the bulk of ESRD patients in the country who lack an eligible ABO compatible renal donor. TPE is an effective tool in reducing ABO antibody titers. With an average of 4–5 TPE procedures pretransplant and 2–3 TPE procedures posttransplants, favorable outcomes can be achieved in majority of the patients. Reducing ABO titers to levels <8 for transplant has no added benefits and can be curtailed to reduce the length of hospital stay preoperatively.

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Conflicts of interest
There are no conflicts of interest.

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