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Original Research Article

Therapeutic Plasma Exchange as a Pre-Conditioning Regimen in ABO Incompatible Renal Transplant- Experience from Largest Transplant Institute in Gujarat, India

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Abstract:

Background: ABO non-identical renal transplantation is becoming increasingly common to overcome the unavailability/ shortage of ABO identical donor(s). This study was conducted to evaluate whether Plasma exchange is an effective method in reducing ABO titers to desired levels in ABO Incompatible renal transplant recipients, as used as a part of desensitization regimen.

Methods: A retrospective observational analysis was done in 11 patients taken for ABOi renal transplant from February 2022 to April 2024. All the 11 patients were treated with Plasma exchange procedures according to the institutional protocol for ABOi renal transplant recipients. Patients with a maximum baseline Anti-blood group (ABO) IgG titer of 512 were considered for such ABOi renal transplants and subsequent plasma exchanges. The purpose of plasma exchange along with immunosuppression was to lower the ABO isohemagglutinin titer to ≤ 4. Statistical analysis was done using Microsoft Excel, Windows. Data were reported as mean ± standard deviation, values and Percentages.

Results: An average of 4.27 pre-transplant plasma exchanges were performed to lower the antibody titer to ≤ 4, along with the standard protocol containing immunosuppressive agents. A maximum and minimum number of plasma exchanges done in each of the patients were 7 and 1, respectively. During the postoperative 1 month follow up the serum creatinine level was maintained at around 1.84 mg/dl in all patients. All patients in the present study showed a high level of compliance with Plasma exchange with only mild adverse reactions.

Conclusion: Plasma exchange can be regarded as a safe and effective method in decreasing the ABO titer to the desired level, in ABOi renal transplant recipients.

Keywords: Plasma exchange, ABOi transplant, renal transplantation.

Introduction

Despite concerted efforts to increase public awareness about the deepening crisis in organ availability, only modest gains in deceased organ donation have been made during the past decade. ABO non-identical renal transplantation is becoming increasingly common to overcome the

unavailability/ shortage of ABO identical donor(s) [1]. On several occasions, close family members are willing to donate but because of different ABO blood groups they cannot be the donor for the recipient. Pioneering centers in ABO- incompatible (ABOi) kidney transplantation have published patient and graft survival rates comparable to ABO compatible transplantations [1–3]. These reassuring outcomes combined with long waiting times for deceased-donor kidneys and the shortage of available living donors have led to a broader implementation of ABOi transplantation. Using a protocol involving a brief escalation in immunosuppression consisting of Plasma exchange and low-dose intravenous immunoglobulin (IVIg), and other immunosuppressive agents, kidneys can be transplanted across any blood group barrier without significant risk of hyperacute rejection, Antibody mediated rejection (AMR) [1], or serious infection. Most hospitals that perform dialysis and kidney transplantation are capable of performing apheresis and measuring isohemagglutinin titers.

This study was conducted to evaluate whether conventional therapeutic plasma exchange along with immunosuppression is effective in reducing the antibody titer of the renal transplant recipient to at or around 4 around the time of transplant and keep it low around 16 until postoperative 4–14 weeks. By keeping a low antibody titer with successive Plasma exchange and immunosuppression, probable AMR is prevented during the perioperative period, where there is maximum possibility of acute graft rejection [5]. We hereby present our experience of eleven ABOi renal transplants where Plasma exchange was done as a part of the preconditioning regimen.

Materials and Methods:

Patient Selection and Immunosuppression Protocol

This retrospective observational study was conducted after obtaining approval from the institutional ethics and scientific committees. A total of 11 patients were taken for ABOi renal transplant from February 2022 to April 2024. For the purpose of this study, a follow-up for a period of 6 months post-transplant was considered.

All the 11 patients were treated with therapeutic plasma exchange according to the institutional protocol for ABOi Renal transplant recipients. Patients with a maximum baseline Anti-blood group (ABO) IgG titer of 512 were considered for such ABOi renal transplants and subsequent plasma exchanges. According to the institutional protocol, the patient, depending upon his antibody titer, would have successive one-volume Plasma exchange procedures on alternate days preoperatively, along with immunosuppressants to lower the antibody titer to, or less than 4. The immunosuppressive agents that were being administered were post Plasma exchange IVIg, Mycophenolate mofetil and Tacrolimus, along with Rituximab starting 14 days before transplant. One dose of Basiliximab was administered on the day of transplantation and another dose on day-4 post-operative. Methylprednisolone was given on the first three consecutive days post-transplant. The dose and duration of these immunosuppressive agents was planned by the treating Nephrologists according to age and disease conditions as three pediatric patients were also included. Four ml of a clotted sample was collected from the patient for antibody titration. Anti-Blood group immunoglobulin G antibody titers against donor ABO blood group antigen was measured in the recipient using Solid Phase Red Cell Assay Technology (Immucor Neo, Werfen, Spain) with Microplate coated with Antihuman globulin. Baseline titration was done before the start of the first procedure. Pre-transplant, to monitor the effect of Plasma exchange, titration was done a day after each Plasma exchange procedure. Post-transplant, in the first week, antibody titration was performed every day and twice a week thereafter for one week.

Plasma exchange

The Plasma exchange was performed with Com. Tec (Fresenius Kabi apheresis equipment, Germany) to lower the antibody titer in the recipient. Before commencing each procedure, the risks and benefits associated with Plasma exchange were explained to the patient and informed consent was taken. In case of pediatric patients informed consent was obtained from parent/guardian. The replacement was planned using a combination of fresh frozen plasma (exclusively AB group plasma) plus normal saline or 5% albumin plus normal saline. The procedure was performed following the Standard operating procedure (SOP) of the department. As a prophylaxis to citrate toxicity, 20 ml Calcium gluconate diluted in Normal Saline was given during the procedure by intravenous infusion. Management of the recipient for citrate effect and other complications were done as per the departmental SOP. All procedures were carried out by team a of Transfusion Medicine Physician and nursing staff. The number of treatments was estimated based on the starting isohemagglutinin titer.

Follow-up (Post-transplant)

Patient follow-up was done twice weekly for the 1st month, weekly for the next 1 month, once in a fortnight till the 3rd month, and monthly thereafter for a period of 6 months. During every visit, renal function tests including serum creatinine and hemogram were monitored. Graft biopsies were

performed whenever indicated such as in case of rising serum creatinine.

Statistical analysis was done using Microsoft Excel, Windows. Data were reported as mean ± standard deviation, values and Percentages.

Results: All 11 patients included in this study were registered for ABOi kidney transplants and were treated with a preconditioning desensitization regimen including Plasma exchange. Table 1 shows baseline characteristics of the recipients and donors. In contrast to a total of 9 male recipients (and 2 female recipients), only one was a male donor (remaining 10 donors were females).

Table 1: Baseline characteristics of ABO-incompatible Recipients and Donors

Variable	Value (Mean ± SD)
Average recipient age (years)	24.90 ± 9.35
Average donor age (years)	51.36 ± 7.74
Recipient gender (%) Male Female	 81.81 18.19
Donor gender (%) Male Female	 9.09 90.91

Majority of the patients (Total 7 out of 11) were O blood group recipients, as seen in Table 2.

Table 2: Recipient and Donor Blood type

Recipient	Donor	N
O	A	4
O	B	3
A	AB	2
A	B	1
B	A	1

Figure 1 Depicts the baseline titer at which plasma exchange was done in each of the recipients. Median baseline antibody titer at which plasma exchange was started was 64.

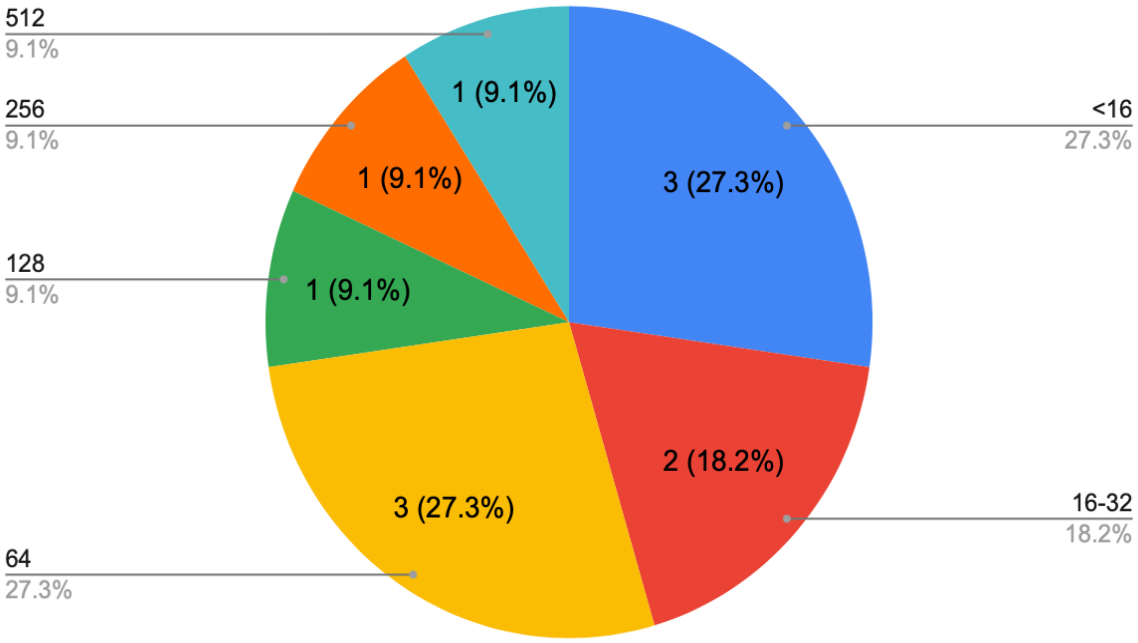

Figure 1: Baseline isoagglutinin AHG titer

Figure 2 shows the number of plasma exchange procedures performed in each patient to lower the titer to ≤4. An average of 4.27 pre-transplant plasma exchange procedures were performed to aid lower the antibody titer along with the standard protocol containing immunosuppressive agents.

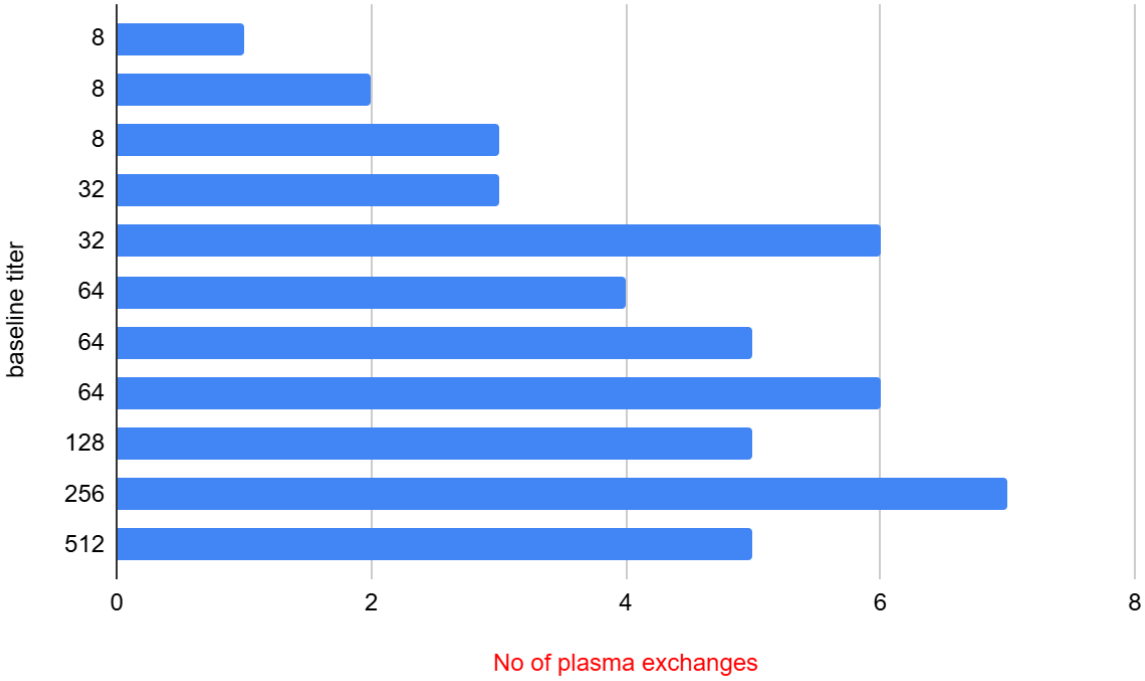

Figure 2: Number of plasma exchange procedures performed in each patient

A maximum 7 Plasma exchange procedures were performed for a patient with a baseline IgG titer of 256 and minimum of 1 Plasma exchange was done for a patient with baseline IgG titer of 8. Figure 3 depicts a linear graph of Baseline titer versus procedures done in all 11 patients. It can be seen that there is a fall in titer after each Plasma exchange done and procedures were done until titer obtained for each patient were ≤4. For the first week post-transplant an antibody titration was performed every day and twice a week thereafter, for 2 weeks. Post-operatively no plasma exchange procedures were done to keep the titer low as this was taken care of by immunosuppressive agents according to institutional protocol.

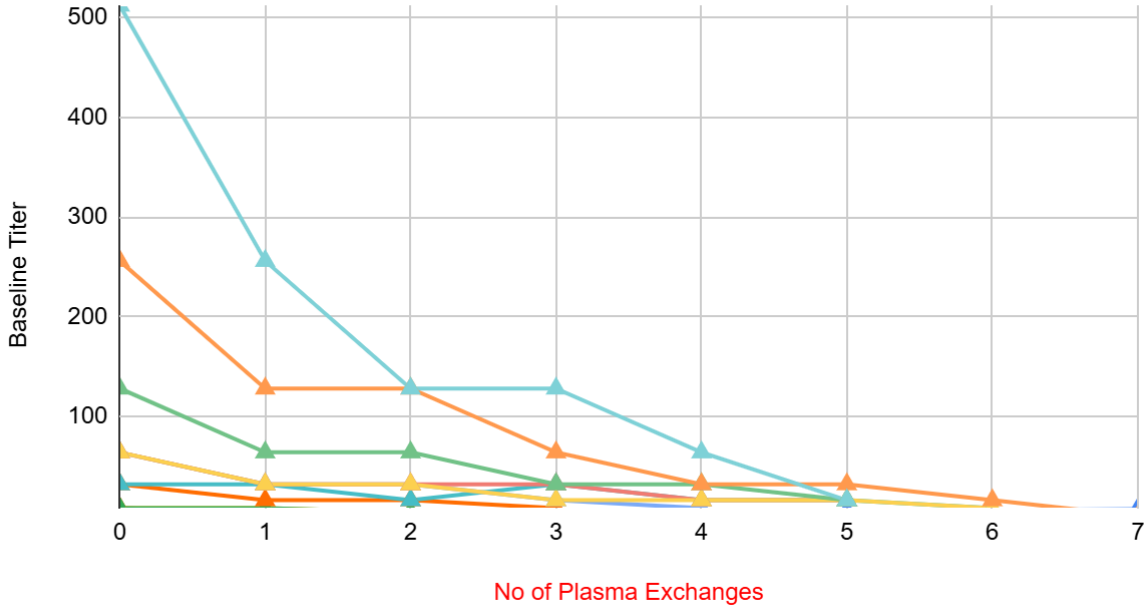

Figure 3: Baseline titer versus Plasma exchange procedures done

Two out of the 11 patients faced acute cellular rejection and died 2 and 4 months post-transplant respectively. During the postoperative 1 month follow up the serum creatinine level was maintained at around 1.84 mg/dl in all patients. Other parameters relevant to graft functions were within normal limits in the remaining 9 patients at 6 months follow-up. None of the patients required dialysis during the first week post- transplant. None of the patients had infectious complications.

One patient had histologically proven antibody-mediated rejection 17 months post-transplant. There was no correlation between antibody titer and rejection. A total of 4 plasma exchange procedures were done in this patient every alternate day to treat ABMR.

Discussion

In the modern transplant era, the gap between the demand and supply of organs is continuously increasing. The biggest obstruction in renal transplantation is the ABO blood group system. As reported in the literature, 30–35% of potential living donors are deferred from organ donation due to ABO incompatibility [6]. ABO incompatible renal transplant cases performed in Japan have demonstrated promising results [3]. Initial attempts to do ABOi renal transplants in the 1950s and 60s were met with high failure. It was only after 1980s that successful use of plasma exchange and splenectomy lead to significant improvement in graft outcomes of ABOi renal transplant recipients. [8] With further improvements in preconditioning protocols including development of apheresis science, it has become possible to do ABOi renal transplants with graft and patient survival at par with ABO-compatible transplants. [2,7]

In our study, the plasma exchange procedure was used as a part of the preconditioning protocol in ABOi Renal transplants. Along with reducing the anti-blood group titer, during plasma exchange procedures complement is removed and this plays a pivotal role in antibody mediated rejection of the transplanted graft [1]. All 11 patients in the present study showed a high level of compliance with Plasma exchange procedures with mild adverse reactions during some cycles. None of the patients developed moderate/severe citrate toxicity, hypotension or other allergic reactions. Therefore, plasma exchange can be regarded as an extremely safe procedure used as a part of the preconditioning regime even at an extremely high titer (in present study, one of the patients had a baseline titer of 512) without splenectomy and its complications.

Patient survival was 81% in the current study. This was 98% in the study by Tyden et al. and 100% in the study by Flint et al. and Lipshutz et al.[9-11] In the UK national registry data of ABOi renal transplant recipients, the patient survival rate at 5 years was 91%.[12]

Most of the studies have reported 5%–33% incidence of AMR in ABOi recipients. In our study, 1 (9%) ABOi recipient developed AMR.

There are few limitations of the present study. This is a retrospective study. The follow-up of patients is quite short. The sample size is small. Despite these limitations, this is one of the largest government aided-center experiences of ABOi renal transplant from India.

Conclusion:

In order to combat the hurdles of ABO incompatibility and increase the donor pool for the ever-increasing waiting list of kidney transplant recipients, plasma exchange can be regarded as a safe and effective method in decreasing the ABO isohemagglutinin titer to the desired level.

Statements and Declarations:

Ethics Approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Institute of Kidney Diseases and Research Centre (Date: 30/10/23./No. GUTS/7th EC/Approved/113/2023).

Consent to participate:

Informed consent was obtained from all individual patients and from patients/guardians in case of pediatric patients included in the study.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions (From 1st to 6th Author in order of their appearance):

1. Dr Amitkumar Vishnubhai Prajapati: contributed towards the analysis of data and interpretation of results.
2. Dr Kamal Vimalbhai Kanodia: guided towards the understanding of post-transplant histopathology of renal transplant recipients and subsequently analysis of such data.
3. Dr Pooja Yuvraj Modi **(Also the primary corresponding author)**: contributed to the concept and design of the study.
4. Dr Himanshu Vallabhbhai Patel: guided towards understanding of the desensitization protocol in ABO incompatible renal transplant recipients and eventually following appropriate methodology
5. Dr Kinnari Bhagwanbhai Vala: guided towards doing plasma exchange procedures in pediatric patients as well as understanding desensitization protocol in pediatric kidney transplant recipients and hence contributing towards the research methodology.
6. Dr Pranjal Ramanlal Modi: contributed towards guiding in the inception of the study and methodology followed as well as interpretation of data.

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