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# Clinical Evidence of Immunoadsorption Column for Desensitization in ABO-incompatible Renal Transplantation (ABOi-RTx) Patients: A Case Series

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## Abstract

**Background:** Immunoadsorption column is used for desensitization of ABO-incompatible (ABOi) kidney transplantation patients. The objective of this case study is to generate clinical evidence of the efficiency of the immunoadsorption procedure as part of the desensitization protocol.

**Methods:** This case series includes data of 10 patients with End-Stage Renal Disease (ESRD) who required desensitization for ABOi living donor kidney transplants. Immunoadsorption (IA) procedure using SECORIM® ABO column was initiated in the dialysis unit of the hospital after rituximab administration. A fresh single use IA column was used for each patient. All 10 patients were discharged from the hospital after kidney transplant. Retrospective data analysis was done to assess the number of IA procedures per patient, number of columns used per patient, kidney function (serum creatinine), anti-A/anti-B antibody titres and adverse events.

**Results:** In total, 25 IA procedures were performed in 10 patients who underwent successful ABO incompatible kidney transplantation. The pre-IA isoagglutinin IgG titre (ranging from 32 to 2048) decreased to the desired level of ≤ 8 with a mean of 2.5 procedures. Serum creatinine reduced from 7.41 ± 2.55 mg/dL (admission) to 1.33 ± 0.58 mg/dL at discharge. Overall, the immunoadsorption procedures were well tolerated. No signs and symptoms of antibody-mediated rejection were reported in any patient. All 10 patients were discharged within a mean of 10.7 days after transplant and continue to do well clinically.

**Conclusion:** Desensitization using SECORIM® ABO IA columns successfully decreased the ABO-isoagglutinin titre levels in all prospective ABO incompatible kidney transplant patients. The IA column was well tolerated.

**Keywords:** Immunoadsorption; ABO-incompatible renal transplantation; Desensitization

## Introduction

Unlike western countries, where cadaver transplant is a norm and a national network manages the transplant waiting list-matching donors to recipients, India has predominantly living-related kidney donors from the immediate family. Due to an ABO blood group mismatch, these "willing" living donors in the family are frequently considered unsuitable. Around three decades ago, ABO incompatibility was thought to be a significant barrier to donor pool expansion. In India, most of the solid-organ transplants are living-donor related. Transplantation of human organs and tissues rules, 2014, restricts organ donations to near-relatives living donors (including spouse, children, siblings, parents and grandparents) to curb organ commercialization. Deceased donor program is still in budding stages and limited to very few institutions. A local organ transplant authorization committee must pre-approve all prospective transplants [1]. ABO-incompatible (ABOi) transplants have arisen as an alternative over time, with multiple studies globally demonstrating that long-term graft survival and patient survival following ABOi transplants are similar to those in ABO-compatible (ABOc) transplants [2]. These comparable results have been achieved through desensitization.

Desensitization for the removal of circulating anti-A/anti-B antibodies evolved from non-selective conventional Therapeutic Plasma Exchange (TPE) to semi-selective Cascade Plasmapheresis (CP)/Double Filtration Plasmapheresis (DFPP) to highly selective Immunoadsorption (IA) [3]. In a nutshell, TPE got involved into IA, pre-transplant desensitization currently relies upon:

- Removing antibodies by means of IA, with the aim of lowering the anti-A/anti-B antibody titre to <1:8 [4].
- Preventing their subsequent synthesis by either pre-transplant splenectomy or rituximab infusion.
- Initiating conventional immunosuppression like rituximab, mycophenolate mofetil, tacrolimus and corticosteroids, 15 days pre-transplantation (-15 Day) and continuing till the day of the transplant (Day 0) [5].

Approximately 45% of IgG is available in the intravascular space and IgG transport from other compartments into the

circulation is reduced within a usual apheresis session of a few hours [6]. Rostaing et al., introduced the possibility of treating larger plasma volumes and thereby prohibiting the rebound of antibodies occurring either through *de novo* synthesis or through redistribution between intra and extravascular compartments, particularly when treatments are performed on consecutive days, even though the rebound is limited, so that the IgG levels are lowered to a greater extent [7].

ABO-mismatched kidney transplantations can be successfully performed without splenectomy and anti-A/anti-B antibodies can be effectively and safely depleted with IA column [8]. In 2005, a new protocol was introduced allowing ABOi kidney transplantations (ABOiKT) without splenectomy that included Rituximab to deplete B-lymphocytes and to prevent rebound of antibodies post-transplant, combined with an antigen-specific apheresis technique for preoperative depletion of circulating anti-A/anti-B antibodies. The antigen-specific filter was first evaluated in 15 patients at the Karolinska University Hospital, Huddinge, with the conclusion that this technique was safe and that anti-A/anti-B antibodies were depleted efficiently [9].

The SECORIM®-ABO employs synthetic carbohydrate antigens immobilized through covalent bonds on porous polymer beads to specifically lower the amount of anti-A/anti-B antibodies. The specific removal of antibodies by SECORIM®-ABO prohibits several side effects compared to other pre-treatment methods, like plasma exchange. Specific antibody removal retains many valuable physiological plasma components. Therefore, SECORIM®-ABO columns offer substantial advantage compared to other methods. The objective of this case series is to present initial findings and patient outcomes in ABOi kidney transplants employing SECORIM®-ABO immunoadsorption columns.

## Materials and Methods

### Setting and participants

Data of ten patients with ESRD who required desensitization for ABOi living donor kidney transplants was collected. IA was initiated in the dialysis unit of the hospital after rituximab administration. A fresh single use IA column was used for each patient. If a patient needed multiple IA sessions, the single use column was re-used multiple times due to cost constraints.

### Demographics

### Immunoadsorption procedure

IA involved centrifugation to separate the patient's plasma which was then passed through a biospecific affinity IA column. The IA column used was SECORIM® ABO columns (Vitrosorb AB, Malmö, Sweden), a selective extracorporeal immunoadsorber, in which one monitor separates the plasma by filtration and the second treats the plasma using selective or specific (anti-A/anti-B/anti-AB) column. The plasma flow through the columns was 40-50 ml/min, at a blood flow of 160-200 mL/min, a usual ratio 1:4. The procedure was variably as long as 10 hrs with 30 mins of preparation.

### Outcomes

Retrospective data analysis was done to assess the number of IA procedures per patient, number of columns used per patient, kidney function (serum creatinine), anti-A/anti-B antibody titres and adverse events.

### Statistical analysis

Descriptive statistics was used to present the data in mean and percentage.

## Results

A total of 25 IA procedures were performed in ten patients who underwent successful ABOi kidney transplantation. **Table 1** provides the demographic information of the patients and donors, including their blood group and relationship. Eight of the 10 (80%) organ donors were female. Serum creatinine at admission was 7.41 ± 2.55 mg/dL.

**Table 1:** Demographic details of patients and donors.

| Case | Age | Gender | Diagnosis/ Treatment | Recipient blood group | Relationship of donor with patient | Donor blood group | Creatinine at admission (mg/dL) |
|---|---|---|---|---|---|---|---|
| 1 | 26 | F | Post ABOiKT recipient | O Rh+ | Mother | B Rh+ | 7.81 |
| 2 | 65 | M | ESRD | O Rh+ | Sister | AB Rh+ | 4.8 |
| 3 | 43 | M | ESRD | O Rh+ | Mother | B Rh+ | 6.8 |
| 4 | 27 | M | Liver related renal allograft recipient (ABOi), HTN with CKD-5 on MHD. | O Rh+ | Mother | B Rh+ | 4.1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5 | 28 | M | Post kidney transplant (liver related ABOi) | B Rh+ | Mother | A Rh+ | 9.43 |
| 6 | 44 | F | HTN, CKD stage 5, recipient ABOiKT | A Rh+ | Mother | AB Rh+ | 8.9 |
| 7 | 41 | M | CKD stage 5, (ABOiKT) | A Rh+ | Sister | B Rh+ | 4.2 |
| 8 | 46 | F | CKD stage 5 on MHD for ABOiKT | B Rh+ | Husband | A Rh+ | 6.2 |
| 9 | 41 | M | Liver related renal allograft engraftment, CKD stage 5-on MHD, ABOiKT | O Rh+ | Father | A Rh+ | 12.4 |
| 10 | 33 | M | ABOiKT | A Rh- | Wife | B Rh+ | 9.41 |

**Note:** ESRD: End Stage Renal Disease; MHD: Maintenance Haemodialysis; CKD: Chronic Kidney Disease; HTN: Hypertension.

The pre-IA isoagglutinin IgG titre ranged from 32 to 2048. Overall, 10 immunoadsorption columns were used for a total of 25 desensitization procedures. The average number of IA procedures required to attain the pre-transplant IgG titre ≤ 8 was 2.5. **Table 2** describes the details of IA procedures performed in these ten patients. Two patients required only 1 IA session, three patients required 2 IA sessions, three patients required 3 IA sessions and two patients required 4 IA sessions. Even on the 4$^{th}$ procedure, the immunoadsorption column was found to be effective. All ten patients were discharged within a mean of 10.7 days after transplant and continue to do well clinically.

**Table 2:** Column immunoadsorption procedure and follow-up details.

| Case | Baseline/First IgG titre | Baseline/First IgM titre | Last IgG titre | Last IgM titre | Total no of IA sessions | Days from surgery to discharge | Creatinine at discharge (mg/dL) |
|---|---|---|---|---|---|---|---|
| 1 | 1:512 | Not measured | 1:4 | 1:8 | 3 | 10 | 1.1 |
| 2 | anti-A=1:512, anti-B=1:256 | anti-A=1:256, anti-B=1:128 | anti-A=1:8, anti-B=1:8 | anti-A=1:2, anti-B=1:16 | 4 | 8 | 0.90 |
| 3 | 1:256 | 1:128 | 1:2 | 1:2 | 3 | 9 | 2.90 |
| 4 | 1:2048 | Not measured | 1:8 | Not measured | 4 | 14 | 1.40 |
| 5 | 1:64 | 1:64 | 1:8 | 1:8 | 2 | 21 | 1.00 |
| 6 | 1:32 | 1:32 | 1:4 | Not measured | 1 | 7 | 1.04 |
| 7 | 1:32 | 1:32 | 0 | Not measured | 1 | 8 | 1.68 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 | 1:64 | 1:8 | 0 | Not measured | 2 | 10 | 0.76 |
| 9 | 1:128 | 1:32 | 1:2 | Not measured | 2 | 10 | 1.09 |
| 10 | 1:64 | 1:4 | 1:4 | 1:2 | 3 | 10 | 1.44 |

Serum creatinine at discharge was 1.33 ± 0.58 mg/dL (mean ± SD). Overall, the immunoadsorption procedures were well tolerated. No signs and symptoms of antibody-mediated rejection were reported in any patient. All the patients were discharged from the hospital within a mean of 10.7 days after kidney transplant and continue to do well clinically.

## Discussion

The introduction of innovative blood group-specific IA columns has enabled a more successful and quick method for ABOi live kidney transplant desensitization. In 2011, Health Canada approved the use of IA single use column for ABOiKT. The advantages of using IA for desensitization include specificity against blood group antibodies, shorter duration of desensitization and reduction of higher levels of anti-A/anti-B titres [10]. In this case series, IA treatment was able to reduce the IgG titre from 2048 to 16 in four IA sessions. ABOi kidney transplants have become a successful "standard of care" substitute for patients who do not have an ABO compatible (ABOc) donor. As per literature, the graft and patient survival rates of ABOi transplants is comparable to ABOc transplants [1].

IA has the capacity to remove immunoglobulins by binding them to selected ligands on the backing matrix surface (membranes or beads) of the adsorber column. One significant advantage of IA over TPE is that no human plasma products need to be substituted. In some adsorbers however, monitoring of fibrinogen is recommended in cases where treatments are performed continuously without any gap [11]. In general, plasma product related risks of intolerability, transmission of infectious agent or compromise of the coagulation system can be avoided with IA technique. Immunoadsorption adsorbers can be divided into non-regenerative and regenerative columns. Non-regenerative columns are single use adsorbers with a single use limit of approximately one patient plasma volume and are mainly indicated in acute autoantibody-mediated diseases. Regenerative adsorber systems consist of column pairs, which are sequentially regenerated during a treatment session and may be reusable. They can treat upto maximum of three plasma volumes of a patient in a single session [11].

These systems are favourable if antibodies must be reduced to low threshold titres, such as those required for the conditioning of kidney transplant recipients with ABO-incompatibility or HLA-sensitization. The use of IA systems in routine care is not universal due to the different regulatory statuses of medical device approval and the economic resources of health care systems [11]. Guidelines for antibody-incompatible transplantation by the British Transplantation Society recommend pretransplant hemagglutination titre ≤ 8 as acceptable [12]. As a result, the current case series accepted pretransplant titres of ≤ 8 as acceptable. This is supported by reports from several centres across India [1].

In this case series, the pre-IA isoagglutinin IgG titre (ranging from 32 to 2048) decreased to the desired level of ≤ 8 with a mean of 2.5 procedures. This case series showed that desensitization using IA column effectively achieved the target anti-A/anti-B titre in all ten patients, thereby allowing successful kidney transplant. In a study by Tiwari et al., the average number of IA procedures used to attain the desired pre-transplant IgG titre ≤ 8 was 3.2 and IA plasmapheresis was universally successful in lowering ABO-isoagglutinin titres to the intended level in all prospective ABOiKT patients [1].

ABOi-KT patients have a high risk of postoperative bleeding, which correlates with the number of preoperative IA sessions conducted [13]. In this case series, none of the patients had post-procedural or post-operative bleeding related complications. Use of immunoadsorption column for desensitization was well tolerated and no severe bleeding events were reported. Serum creatinine reduced from 7.41 ± 2.55 mg/dL during admission to 1.33 ± 0.58 mg/dL at discharge. This indicates that kidney function normalized within 2-6 days of ABOi kidney transplant. In a similar study by Junker et al., thirteen patients prepared for ABO blood group-incompatible living donor kidney transplantation (ABOi LDKT) with IA with heparin anticoagulation had no major bleeding or other significant complications [14]. Smaller quantities and electrolyte shifts occur with desensitisation with heparin anticoagulation. This could be beneficial for people who are susceptible to clinically relevant volume overload. As a result, extra haemodialysis for volume adjustment may be avoided in the days leading up to the transplantation surgery. Heparin clearance is reduced in individuals with severe kidney disease, especially at higher doses, but it can still be used safely in these cases [14].

Tiwari et al., reported no adverse events in their case series [1]. In this case series, the IA procedure found hope. No signs and symptoms of antibody-mediated rejection were reported in any of the patients. Though the single use column was used several times for one patient due to economic constraints, the IA column was effective and safe even on the fourth procedure. The efficiency level and outcomes of using one IA column multiple times was equivalent to single use outcome.

Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) indicates column immunoadsorption removal of anti-A/anti-B antibodies before ABO-incompatible renal transplantation [15]. The Indian consensus on ABO incompatible kidney transplantation made certain recommendations [16]. These are:

- Assessment of one AB titre before subjecting patient to AB removal.
- Post-Plasmapheresis (PP) titres must be investigated between 2 and 12 hrs.
- If cost and accessibility are not a concern, IA should be the preferred desensitization protocol.

Renal transplantation is the best treatment form for patients with chronic kidney disease requiring renal replacement therapy. In developing countries such as India, transplant options are limited and ABO incompatibility remains an important limiting factor among the living donors. It leads to rejection of around 35% living kidney donors [17]. Living donor kidney transplantation is traditionally planned in accordance with the rules of blood group compatibility [18]. Unintentional ABO barrier breaches have resulted in immediate or irreversible graft losses. ABOiKT strategies have changed over the span of two decades from splenectomy to selective antibody elimination using IA approaches. ABOiKT strategies vary around the world in terms of antibody removal techniques, approved and target antibody titres, antibody detecting methods and immunosuppression maintenance. The majority of European preconditioning protocols rely on IA techniques with antigen-specific columns [19,20].

Desensitization using immunoadsorption has a clear advantage with respect to the avoidance of exposure to blood products (albumin and/or plasma) and preservation of clotting factors (reducing the risk of bleeding) and all other immunoglobulins as IA specifically removes only anti-A/anti-B antibodies (avoiding further unnecessary immunosuppression) [21]. This approach avoids the cost of blood products and any potential side effects relating to their use. Because patient plasma undergoes filtering after which it is transferred to the patient during IA, any circulating drugs are not eliminated [22]. Introduction of IA columns in ABOi preconditioning protocols has led to considerably good graft and recipient outcomes. Despite its high cost, antigen-specific IA has the advantage of efficiently depleting circulating antibodies while preserving protective antibodies and other critical plasma components such as coagulation factors.

Since this was a retrospective data analysis of ten cases, obtaining complete medical records was difficult and thus, some patient details are missing including vital signs. Conducting a multicentric, real-world study with a larger patient population will be helpful in assessing the efficiency and safety of the IA column.

## Conclusion

In this case series, desensitization using IA column effectively achieved the target anti-A/anti-B antibody titre in all ten patients. The use of IA columns for desensitization in prospective ABOiKT patients allowed successful kidney transplant including good graft and recipient outcomes. The IA column for desensitization reduced higher levels of antibody titres and was well tolerated.

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