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Red cell alloimmunization & role of advanced immunohaematological support in liver transplantation

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***Background & objectives*: Transfusion support forms an integral part of liver transplantation programme. Advanced immunohaematology services are required to deal with complex serological problems that can complicate transfusion therapy in these patients. Here, we report on red cell alloimmunization and presence of alloimmunization in donors and patients undergoing liver transplantation in a tertiary care hospital in north India.**

***Methods*: Records of 1433 liver transplants performed from January 2009 to March 2015 were retrieved and reviewed. Antibody screening was performed both for liver donors, and recipients and antibody identification was performed for the screen-positive patients.**

***Results*: Of the 1433 liver recipients, 32 (2.3%) developed antibodies. Seventeen patients had one or more alloantibodies, five had autoantibodies with an underlying alloantibody and 10 had only autoantibodies in their plasma. The overall alloimmunization rate was 1.5 per cent with 25 alloantibodies identified in 22 patients. Anti-E was the most common specificity identified.**

***Interpretation & conclusions*: The presence of alloantibodies can complicate transfusion therapy in patients undergoing liver transplantation, who are already at a high risk of being heavily transfused owing to the nature of surgery and the haemostatic dysfunction from chronic liver disease. Therefore, screening for irregular red cell alloantibodies combined with a rational blood transfusion policy may be essential for these patients.**

Key words Alloantibodies - alloimmunization - liver transplant - red blood cell antigens- serological problems - transfusion support

Orthotopic liver transplantation is a life-saving procedure for patients with end-stage liver disease of various aetiologies starting from alcoholic cirrhosis to hepatitis B or C induced liver failures[1]. Transfusion support forms an integral part of this programme by not only providing quantitative support in terms of blood and blood components but also qualitatively by addressing the complex serological problems and immunological effects of transfusion that act as a challenge. A well-equipped and advanced immunohaematology laboratory is a cornerstone for the success of solid organ transplants[2,3].

Alloimmunization to red blood cell (RBC) antigens is a complication arising out of transfusion of red cells and in turn complicates further transfusion therapy[4]. Patients awaiting liver transplant are

likely to be transfused blood and blood components and are therefore, at a risk of alloimmunization[5]. Alloantibodies, if left unidentified, may lead to delayed haemolytic transfusion reactions which can further raise the bilirubin levels and also worsen the pre-existing anaemia and liver function in the already compromised patients[4]. From the transfusion service perspective, difficulty in finding cross-match compatible blood and delays in blood arrangement are inevitable, if immunohaematological workup is not performed beforehand. Finding appropriate antigen negative blood may be a time-consuming task and compatible units may not be available in emergent situations[6].

Centres performing solid organ transplants should be equipped with advanced immunohaematology laboratory and trained personnel for handling complex red cell serological problems. However, there is a paucity of literature on immunohaematological and transfusion support for liver transplants from this region. We present an overview of our experience as transfusion and immunohaematology support service in a tertiary care hospital on red cell alloimmunization and presence of alloimmunization in donors and patients undergoing liver transplantation.

Material & Methods

Records of 1433 consecutive liver transplants performed at Indraprastha Apollo Hospital, New Delhi, India, from January 2009 to March 2015 were retrospectively reviewed and analyzed from the departmental records. For the margin of error at three per cent, confidence level of study at 95 per cent and power at 80 per cent, a minimum of 21 patients were required to evaluate the red cell alloimmunization and the role of advanced immunohaematological support in liver transplantation. Demographic details such as age and gender were retrieved from the hospital records. Irrespective of the ethnicity, all adult patients undergoing the transplant were included. Except for the patients under 18 yr of age and those undergoing combined liver and kidney transplants, all other patients undergoing liver transplantation were included and analyzed. With the group and screen policy[1] in place for all patients, blood grouping and antibody screening were performed for all donors and recipients on the fully automated immunohematology analyser (Galileo, Immucor Inc., USA) in the department of Transfusion Medicine, Indraprastha Apollo Hospital, New Delhi. Antibody identification was performed for the screen-positive patients using cell panels by the SPRCA technology (Capture-R Ready-ID, Immucor Inc., Norcross, USA). For blood grouping, antibody screening and identification, samples were collected in ethylene diamine tetra acetic acid (EDTA) vials. Once, the alloantibody specificity was determined, corresponding antigen negative, anti-human globulin compatible units were reserved for the patients.

In patients where, alloantibodies against Rh (C, c, E, e) or Kell (K) antigen system were detected, appropriate antigen negative units were directly picked up from the inventory for cross-matching. For antibodies against other minor red cell antigen systems, ABO group specific units were typed serologically to find antigen negative units. The immunized cases were discussed with the transplant team beforehand so that transfusion requirements could be anticipated in advance and adequate blood units reserved.

Results

Of the 1433 liver recipients, 32 (2.3%) developed antibodies. These included 18 males and 14 females, with a mean age of 48.7 yr, ranging between 31 and 66 yr.

Of the 32 recipients, 17 (53.1%) had one or more alloantibody, five (15.6%) had autoantibodies with an underlying alloantibody and 10 (31.3%) had only autoantibodies in their plasma. The overall alloimmunization rate was 1.5 per cent with 25 alloantibodies identified in 22 patients. All the alloantibodies identified were clinically significant. Alloantibodies against the five major Rh antigens namely D, E, e, C, c, were the most frequent (81.8%) with anti-E being the most common specificity identified (13 patients, 72.2%) (Table).

Table. Specificity and frequency of red cell alloantibodies in liver transplant recipients (n=1433)

Blood group system	Blood group antibody	Number	Frequency (%)
Rh	Anti-E	13	0.91
	Anti-c	3	0.21
	Anti-C	1	0.07
	Anti-D	1	0.07
Kell	Anti-K	1	0.07
Kidd	Anti-Jk^a	4	0.28
MNSs	Anti-M	1	0.07
Duffy	Anti-Fy^b	1	0.07

Fifteen of the 18 males and 12 of the 14 females had a history of prior red cell transfusions. Significant obstetric events which could have sensitized the females were reported in 13 cases.

Packed red cell usage: A total of 289 packed red cell units were arranged for the 22 alloimmunized liver recipients, with a mean of 13.1 units per patient, while 197 units were issued during the transplant, with a mean of 8.9 units per patient (range: 2-22 units).

Ten Fy^b antigen negative units were arranged after typing 68 units for the patient with anti-Fy^b, while 92 units were crossmatched to reserve 10 M antigen negative units for the patient with anti-M. In all, 32 units were reserved for the four patients with anti-Jk^a antibody after typing 145 units. The other antigen negative units were picked up for crossmatch from the inventory of Rh and Kell typed donor units. Patients with warm autoantibodies with an underlying alloantibody were issued corresponding antigen negative blood crossmatched with the adsorbed plasma.

Alloimmunization in liver donors: Ten of the 1433 liver transplants performed were from cadaveric donors. Among the 1423 living donors, nine (0.6%) were immunized (6 males & 3 females) with a mean age of 28.5 yr (range 19-41 yr). Of these nine donors, only two (0.14%) had alloantibodies. One was sensitized by previous transfusion forming anti-E while the other was an Rh (D) negative female with no history of transfusion but possibly sensitized during a previous obstetric event with anti-D. In the remaining seven, only autoantibodies were found.

A total of four red cell units (2 each) were arranged for both alloimmunized liver donors while none were issued.

Discussion

Alloimmunization to RBC antigens can significantly impact transfusion support of patients undergoing solid organ transplantation. There is a need for universal antibody screening in all such patients as part of pre-transfusion testing, which helps to identify atypical antibodies and plan for appropriate transfusion support well in time[7].

We have previously reported alloimmunization rates in general patient population at our centre as 0.49 per cent[8], while the average red cell transfusion requirement in liver transplant surgeries at our centre have been reported as 8.48 units per patient[9]. Globally, alloimmunization in general patient population has been reported between 0.46 and 3 per cent[10,11] whereas the rates among liver transplant patients have been reported from 5.75 to 23 per cent[7,12,13]. In this analysis alloimmunization rate of 1.5 per cent was observed in liver transplant recipients which was relatively lower than that reported globally. Luzo *et al*[7] reported a higher incidence of alloimmunization and attributed this to ethnic heterogeneity in their population. Shariatmadar *et al*[12] followed up liver transplant recipients postoperatively for the development of alloimmunization which was attributed to a higher alloimmunization rate as compared to ours.

In our study two liver donors were found to be alloimmunized due to previous sensitizing events. There is always a possibility that the recipients of these alloimmunized donors might face delayed serological transfusion reaction if positive for the corresponding antigen via the passenger lymphocyte syndrome. It is advisable to transfuse recipients of such alloimmunized donors with corresponding antigen negative units[1,14,15]. Antibodies against Rh and Kell blood group antigens have been reported as most common in general patient population[7] as well as in liver transplant recipients[13,16]. Our findings were similar to these results with 81.8 per cent (18 out of 22) of the antibodies in alloimmunized patients, and 100 per cent of the antibodies in alloimmunized donors were against the Rh system. Among the alloantibodies directed against the Rh system antigens, anti-E was the most common.

Antigens M, Fy^b, and Jk^a were all relatively more prevalent in our donor population with frequencies of 88.7, 57.6 and 81.5 per cent respectively, as reported in a previous study from our centre[17]. The availability of this antigen frequency data guided us in estimating the number of red cell units needed to be typed to get an antigen negative unit for the six patients who were immunized against these antigens.

The presence of alloantibodies can complicate transfusion therapy in patients undergoing liver transplants, who are already at a higher risk of being heavily transfused owing to the nature of surgery and the haemostatic dysfunction from chronic liver disease[18]. Furthermore, there are reports documenting issue of antigen positive units to alloimmunized liver transplant patients leading to mortality in three patient[19]. Alloantibodies may also affect liver transplant outcomes and can contribute to higher incidences of early death[12,18,19]. Therefore, screening for irregular

red cell alloantibodies combined with a rational blood transfusion policy is essential in these patients.

RBC alloimmunization can present a special challenge to solid-organ transplantation. Early serologic testing of the recipient pre-transplant as well as pre-transfusion and prompt communication between the transfusion service and transplant team may facilitate successful transfusion management of these patients.

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***Conflicts of Interest*:** None.

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