Pediatric ABO-incompatible Living Related Donor Liver Transplantation: Experience from Indian Subcontinent

We present our experience with pediatric ABO-incompatible liver transplantation in India. Data of patients <18 years of age undergoing ABO-incompatible liver transplantation in our hospital between January, 2011 and November, 2018 were analyzed. Plasmapheresis was done pre-transplant till antibody titer was <16 units. Rituximab/Intravenous immunoglobulin was used for immunosuppression, in addition to standard drugs (mycophenolate mofetil, steroids, and tacrolimus). Out of 203 patients that underwent liver transplant during this period, 8 underwent ABO-incompatible liver transplantation; 4 (3 boys) had blood group O+ve. Median (range) age was 28 (7-91) mo, PELD score was 24.5 (14-42), and pre-transplant antibody titer range was 1:32-1024. Number of plasmapheresis sessions required ranged from 1-6. Post-operatively two patients had rise in antibody titer >64 requiring plasmapheresis. All 8 patients survived without rejection/biliary issues. Mean (range) of post-transplant hospital stay was 19.1 (13-22) d and follow-up period was 38.1 (7.1-84.4) mo. Pediatric ABO-incompatible liver transplantation can be successfully performed using plasmapheresis with optimal immune-suppression and vigilant post-op monitoring.

Keywords: Immunoadsorption, Outcome, Plasmapheresis, Rituximab.

Due to shortage of cadaveric organ donation, living donor liver transplantation (LDLT) is the primary form of liver transplantation (LT) in India. In the LDLT scenario, donors are restricted to family members and it is not always possible to find a healthy blood group-compatible donor in time. Liver transplant across the ABO blood group barrier is a promising approach in such patients. Antibody-mediated rejection along with biliary and vascular complications are the usual limiting factors in ABO-incompatible (ABOi) LT [1]. Determining optimal immunosuppression to avoid complications in ABOi LT is challenging. Desensitization with use of plasmapheresis and anti-CD20 monoclonal antibody (rituximab) plays an important role in successful outcome of ABOi LT [2]. Our aim was to study the course and outcomes of pediatric ABOi LT.

Data of all patients (<18 years) undergoing ABOi LDLT at our hospital, India between January, 2011 and November, 2018 were retrospectively analyzed. ABOi LT was performed only in cases where compatible related donors were unavailable even after exploring option of swap transplant between two families. Informed consent was taken for ABOi LDLT. Hospital liver transplant committee clearance was obtained. Demographic details, primary diagnosis and severity of liver disease using Pediatric end-stage liver disease (PELD) score were noted. Recipient and donor blood group and pre-transplant antibody titres were recorded. Surgical details and post-operative course including antibody titres, duration of ICU and hospital stay, incidence of hemolysis, rejection, biliary and vascular issues and infections were recorded.

For immunosuppression, all patients were started on mycophenolate mofetil (MMF) one week pre-transplant. After 2016, rituximab was added to the institutional protocol for pre-transplant preparation CD19 levels were in those receiving rituximab monitored before and post LT. Plasmapheresis was done pre-LT on alternate days to reduce antibody titre16. Prior to 2012, conventional plasmapheresis with AB blood group fresh frozen plasma was done. Thereafter with the availability of 2A column filter (Evaflux 2A column; Kawasumi Laboratories) at our institution, cascade plasmapheresis was performed. In cases where conventional/cascade plasmapheresis failed to decrease antibody titre <16 or when urgent LT was needed, plasmapheresis with immune-adsorption technique using Glycosorb/ Adsopak filter was done. Prior to 2016, intravenous immunoglobulin (IVIG) was given for first five days post-operation to prevent antibody-mediated rejection. After 2016, IVIG was no longer used prophylactically, but reserved only for treatment of antibody-mediated rejection. Post-operatively triple immunosuppression with MMF, steroids and tacrolimus was administered. Target trough level of tacrolimus was 10-12 ng/mL in the first month post-LT. Antibody titers were closely monitored and the threshold to do plasmapheresis was a titer ≥64 for up to two weeks post-LT.
A total of 203 pediatric LDLT were performed at our institute during the study period; 8 these were ABOi LT. All 8 (3 males) patients had underlying cholestatic liver disease of which 5 had biliary atresia. Median (range) age was 28 (7-91), months and median (range) PELD score was 24.5 (14-42). Four of the 8 recipients had blood group O, two each had blood group A and B. Pre-transplant baseline antibody titer ranged from 32 to 1024 units. Mean (range) pre-transplant hospital stay was 12.5 (1-44) days. Number of pre-transplant plasmapheresis sessions ranged from 1-6 and was proportional to the initial titer. Conventional plasmapheresis was used in the first two patients, prior to 2012. Thereafter, cascade plasmapheresis was used for 5 cases; immune-adsorption was used in 2. One patient had high initial antibody titer of 1024 units which reduced to 256 units after two sessions of cascade plasmapheresis. There was a subsequent rise of antibody titer to 1024 units during an episode of sepsis. After recovery, three sessions of immune-adsorption plasmapheresis decreased antibody titer to 8. Another patient underwent ABOi transplant in limited preparation time with a domino graft using the explanted liver of a child of maple syrup disease undergoing liver transplant using immune-adsorption plasmapheresis. A single cycle decreased the antibody titer from 128 to 4 units. IVIG was used in first 3 cases, prior to 2016 and rituximab was used thereafter in 3 patients. Two of these were between 2-8 years with risk factors of high initial antibody titer (> 256) and re-transplantation.

Post-transplant, mean (range) ICU stay was 7.3 (5-11) days and post-transplant hospital stay was 19.1 (13-22) days. Postoperatively two patients had rise in antibody titer up to 256 (on sixth day) and 64 (on seventh day), respectively which required 4 and 3 sessions of cascade plasmapheresis to reduce antibody titer <32. One patient developed E. coli sepsis which responded to antibiotics. Two patients developed vascular complications. No biliary or bowel complications were noted. Two patients developed hemolysis (peripheral smear changes, LDH >1000 U/L and reticulocytes >2%) which resolved spontaneously. All eight patients survived without any evidence of acute/chronic rejection. The mean (range) follow-up period was 38.1 (7.1-84.4) months.

Pediatric graft survival rates were reported similar after ABOi LT and blood group compatible LT, whereas graft survival in adults after ABOi LT were lower [4]. Antibody-mediated rejection is a catastrophic complication which can occur in the first 2-4 weeks. The risk of ischemic cholangitis, bile leak, biliary stricture formation, and hepatic artery thrombosis is higher in ABOi LT [5]. The approach in ABOi LT is directed towards reducing antibodies pre-transplant and inhibiting its production post-transplant for at least 2-4 weeks by effective immunosuppression [6].

Plasmapheresis is the most effective way to control humoral antibody response to prevent rejection [7]. We used all the methods of plasmapheresis: conventional, cascade and immune-adsorption. IVIG inhibits complement and T-cell-mediated graft injury by FC-receptor-dependent B-cell apoptosis [3]. With availability of effective drugs like rituximab the use of prophylactic IVIG has become less relevant. However, IVIG is more effective for treating antibody-mediated rejection as exerts faster effects than rituximab [3]. We used CD19 as a surrogate marker for patients who received rituximab as it mirrors the expression of CD20 [8].

Recipient blood group O is the most susceptible group antibody-mediated rejection [9]. Although, half of our patients had blood group none of them developed antibody-mediated rejection or biliary complications probably due to optimal immunosuppression. The vascular complications seen in two patients were diagnosed early and timely surgical management prevented any permanent hepatic damage, thus emphasizing the importance of vigilant postoperative monitoring.

Our experience in pediatric ABOi LT suggests that it is a promising alternative in India when compatible graft donor is unavailable.

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