HLA Alloimmunization and Blood Requirements in Orthotopic Liver Transplantation

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ORTHOTOPIC LIVER transplantation (OLT) is often accompanied by massive blood loss due to portal hypertension, difficult dissection as a result of previous abdominal surgery, and coagulation abnormalities. Major alterations of the coagulation factors such as prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), decreased fibrinogen levels and thrombocytopenia have already been documented in patients undergoing OLT.[1-3] Moreover, problems like fibrinolysis and consumption coagulopathy have been demonstrated to play an important role in blood coagulation system alterations during such an operation;[4,5] these factors often necessitate large quantities of blood products during OLT, despite recent advances.[2,6-8]

Packed red blood cells (RBC), fresh frozen plasma (FFP), platelets (PLT) and cryoprecipitate (CRY) represent the different blood fractions commonly transfused during OLT. The relation between massive blood use in OLT, morbidity[9] and mortality[10,11] has already been described.

We have investigated the role of HLA alloimmunization in intraoperative blood transfusion requirements during OLT. Alloimmunization can result from previous exposure to HLA antigens through transfusion, transplantation and pregnancy and is usually detected by serum screening for lymphocytotoxic antibodies.

HLA plays a significant role in blood transfusions especially those involving platelets. It is well known that PLT express class I HLA antigens and specific alloimmunization to these antigens is a major cause of refractoriness in thrombocytopenic patients to platelet transfusions.[12-14]

Our results demonstrate that HLA alloimmunization has a major effect on blood transfusion requirements during OLT. Intraoperative blood use was significantly increased in alloimmunized liver transplant recipients. This retrospective study indicates that pre-transplant screening of liver candidates is useful in estimating blood transfusion requirements during OLT.

PATIENTS AND METHODS

Between March 1980 and December 1986, 1053 OLTs were performed in the Departments of Surgery of the University of Pittsburgh and the Baylor Medical Center in Dallas. The case series includes first (821), second and third OLTs.

Two groups of adult patients were selected from our liver transplant file on the basis of panel reactive antibody (PRA) of pre-transplant serum as determined by lymphocytotoxicity testing with a panel of 45-60 HLA typed donors as previously described.[15] One group of highly alloimmunized patients (n = 25) had PRA values greater than 70% and the second group of nonsensitized patients (n = 26) had PRA values of 0%. Patients who had undergone major surgery immediately prior to transplantation and patients with intraoperative bleeding due to technical reasons were excluded. Both groups of patients were randomly selected except for PRA. All cases were first transplants and there were no significant age, weight and pathology differences between the two groups (Table 1). Heparin was never used pre- and/or intraoperatively. Intraoperative blood replacement was determined by thromboelastrographic monitoring as previously described.[2] Intraoperative infusion of RBC, PLT, FFP and CRY was retrospectively analyzed, in each group.

Statistical analysis was done by Student's t and Mann Whitney U test. Data are shown in mean values ± standard error.

RESULTS

Highly sensitized patients (70% PRA group) received intraoperatively 21.1 ± 3.7 units of RBC and 17.7 ± 3.2 units of PLT, significantly more than nonsensitized patients (0% PRA group) who received 9.8 ± 0.8 units of RBC and 7.5 ± 1.5 units of PLT (RBC: $p = 0.002$; PLT: $p = 0.003$) (Fig. 1). In addition, transfusion of FFP and CRY was significantly higher in the 70% PRA group than in the 0% PRA group (FFP: 20.4 ± 4.2 vs 9.2 ± 6.0, $p = 0.006$; CRY: 8.3 ± 2.5 vs 3.6 ± 1.2, $p = 0.026$) (Fig 1).

Despite the larger PLT substitution in the 70% PRA group, as shown in Figure 1, PLT counts dropped from 106,826 ± 13,714/mm^3 preoperatively to 71,043 ± 7,816/mm^3 postoperatively ($p = 0.006$). In contrast, the 0% PRA group had similar pre- (119,600 ± 18,688/mm^3) and postoperative (114,000 ± 14,617/mm^3) PLT counts ($p = 0.55$).

PT, APTT, hematocrit, and fibrinogen level showed no significant differences between both groups (data not shown).

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Supported in part by research grants from the Veterans Administration and Project Grants HL-35069 and AM 29961 from the National Institutes of Health, Bethesda, Maryland, USA.

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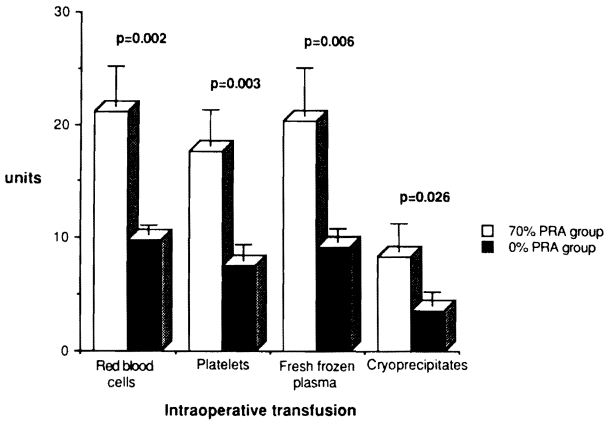

Fig 1. Intraoperative transfusions of red blood cells, platelets, fresh frozen plasma, and cryoprecipitates in 25 highly sensitized (70% PRA group) and 26 non-sensitized (0% PRA group) patients.

DISCUSSION

Management of bleeding represents one of the most important aspects of OLT. Often OLT candidates have severe coagulation disturbances and the frequent presence of portal hypertension makes surgical hemostasis exceedingly difficult.[3,6]

In several other reports the number of RBC untis was used as a variable to evaluate intraoperative bleeding.[9-11] In our previous series of 87 OLTs, the range for RBC units was very large, from 3 to 251, with a median of 24 and a mean of 43 units;[11] consequently, many attempts have been made to prevent the causes of bleeding during OLT. In addition to the importance of meticulous care in checking and suturing each potential source of bleeding during the operation,[3,6] in the last years many efforts have been made to develop devices and strategies to aid in managing intraoperative bleeding. The veno-venous by-pass equipped with heparin coated tubes, inhibiting clot formation without causing generalized heparinization, has been very effective in reducing portal and caval hypertension and consequently blood loss during the anhepatic phase.[16] The infra-red sapphire-headed coagulator has been effective in reducing bleeding from difficulty managed sites.[3]

Intraoperative monitoring by thrombelastography in the last four years has reduced blood infusion volume by 33% and increased blood coagulation stability without adding blood products.[2] Also, the appropriate use of epsilon-aminocaproic acid in patients undergoing OLT[17,18] is very effective in treating fibrinolysis and associated generalized oozing.

Despite advances, bleeding problems are still one of the major concerns in OLT. During OLT a generalized oozing may develop from all the cut surfaces, a phenomenon not related to mechanical trauma. This lengthens hemostasis time and necessitates larger amounts of blood products. The quantity of blood used correlates negatively ($p = 0.0005$) with survival as demonstrated in our previous investigations.[10,11]

Table 1. Patient Population in the Non-Alloimmunized Group (0% PRA) and in the Highly-Alloimmunized Group (70% PRA)

Patient Population	% PRA Group	70% PRA Group
Age (years)	44.1 ± 8.9	44.3 ± 10.8
Weight (Kg)	67.5 ± 16.2	63.1 ± 16.1
Primary biliary cirrhosis	6	6
Chronic active hepatitis	7	9
Laennec's disease	6	3
Fulminant hepatitis	2	1
Antitrypsin deficiency	1	3
Others	4	3

In this study we present evidence suggesting that lymphocytotoxic antibodies in OLT patients are associated with increased intraoperative blood transfusion requirements. Highly sensitized patients with PRA values equal to or greater than 70% received greater quantities of RBC, PLT, CRY and FFP intraoperatively than did the 0% PRA patients.

Lymphocytotoxic antibodies are generally specific for HLA antigens. HLA alloimmunization is a major cause of platelet refractoriness in thrombocytopenic patients requiring transfusions. Such refractory patients respond poorly to random ABO compatible platelets.[14] Our data suggest that platelet transfusions are also less effective in correcting the bleeding problems of highly sensitized patients undergoing OLT. This is more apparent from our findings that although the 70% PRA patients received larger quantities of PLT, they had significantly lower PLT counts postoperatively. This lower PLT count might be due to the "innocent bystander" effect whereby the patient's own PLT become involved in the immune clearance of incompatible PLT.[12] Thus, in certain alloimmunized patients, random PLT transfusions would not only be ineffective, but might also worsen the bleeding problems during surgery.

Our data also show a close correlation between the amounts of transfused PLT and RBC in the 70% PRA group, but not in the 0% PRA group. This can be explained by the possibility that PLT tranfusion in the 70% PRA is not effective in correcting intraoperative bleeding, leading to increased RBC substitution in the 70% PRA group.

The decreased coagulation status in the 70% PRA patients is indicated by the different requirement for plasma replacement and substitution with concentrated fractions of coagulations factors. The 70% PRA group needed significantly higher substitution with FFP and CRY than the 0% PRA group.

In conclusion, our findings suggest that routine screening for HLA alloimmunization should be done in every OLT candidate as well as in all patients undergoing major surgical treatments who may require intraoperative PLT transfusions. Highly sensitized patients are at risk of developing refractoriness to intraoperative PLT transfusions with subsequent uncontrollable bleeding. These patients might benefit from transfusions of histocompatible PLT to achieve sufficient hemostasis.

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