Low plasma fibrinogen levels and blood product transfusion in liver transplantation

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ABSTRACT

Aim. Risk of bleeding in liver transplantation is determined by surgical technique, preoperative hemoglobin and antifibrinolitic therapy. We hypothesize that keeping these confounders factors identical, preoperative plasma fibrinogen level of ≤2 g/L influenced on blood product requirements.

Methods. Adult patients underwent orthotropic liver transplantation (LT) during the period between January 1998 and December 2009. Cases were selected according to a propensity matching analysis meeting the following criteria: surgical vena cava preservation, tranexamic acid administration and hemoglobin range between 90 to 120 g/L. Intraoperative management was protocolized. The main variable was the percentage of patients that do not require red blood cells (RBC's).

Results. Six hundred sixty-four patients with LT, 208 excluded, 266 who cannot be matched, the analysis was performed on 190 patients. Two cohorts: Low fibrinogen (≤2 g/L) (61 cases) and standard fibrinogen (>2 g/L) (129 cases) were analyzed. Preoperative platelet count (73.5±52 *vs.*. 104±65; 10^3/mm^3) was different in contrast to the hemoglobin (104.2±8.6 *vs.* 105.6±8.3; g/L). Use of RBC's resulted significantly higher in the low fibrinogen group (median, 3 *vs.* 2). The number of patients with no blood product requirements was fewer in the low fibrinogen group (8 cases, 13% *vs.* 45 cases, 35%). The critical level of plasma fibrinogen (1 g/L) was reached after graft reperfusion in 7 cases (5.5%) in the standard fibrinogen group *vs.* 24 cases (39%) in the low fibrinogen group.

Conclusion. Our data suggest that preoperative plasma fibrinogen level of ≤ 2 g/L increases requirements for blood products during the surgical procedure of liver transplantation. *(Minerva Anestesiol 2013;79:1-2)*

Key words: Blood coagulation factors - Blood component transfusion – Liver transplantation.

Risk of bleeding and transfusion in liver transplantation (LT) are determined by severity of liver disease, surgical technique, preoperative hemoglobin value and antifibrinolitic therapy.[1-4] In cirrhosis, despite the low levels of haemostatic proteins, thrombin generation is preserved.[5] As a result of thrombin action, large amounts of fibrinogen are captured by the platelet glycoprotein IIb-IIIa receptor and converted to fibrin, which is polymerized by thrombin-activated FXIII and simultaneously cross-linked by alfa2-antiplasmin to stabilize the thrombus.[6] Failing in fibrin polymerization facilitates the release of thrombin and factor X from the local thrombus to systemic circulation, promoting the factor consumption and surgical bleeding.[7]

Correlation of conventional coagulation tests and bleeding events during LT still remains unclear.[8] Two main factors influence the level of plasma fibrinogen during LT: consumption related to the coagulation process because of bleeding and hemodilution mainly at reperfusion of the liver graft. We hypothesize that keeping confounders factors for transfusion identical, patients with a preoperative plasma fibrinogen level

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of ≤2 g/L will increase surgical bleeding and lead to increase requirements for blood products.

Materials and methods

Adult patients undergoing orthotopic liver transplantation from deceased donors during the period between January 1998 and December 2009 at one center were considered for analysis. The Clinical Research Ethics Committee (IRB00005523) has revised this manuscript for its publication.

Cases were selected according to a propensity matching analysis meeting all three following criteria: surgical technique of vena cava preservation, antifibrinolitic therapy and preoperative hemoglobin range remaining between 90 to 120 g/L. Antifibrinolitic therapy was based on 10 mg/kg bolus of tranexamic acid during anesthesia induction followed by 10 mg kg^{-1} hour of continuous infusion kept until two hours after graft reperfusion.[9] Contraindications to tranexamic administration were: Budd-Chiari syndrome, acute liver failure, early retransplantation, simultaneous kidney and liver transplantation, intraoperative dialysis and primary familial amyloidotic neuropathy.[9] Two cohorts of patients were created based on preoperative plasma fibrinogen: Low fibrinogen (≤2 g/L) and standard fibrinogen (>2g/L).

Management during the procedure was protocolized for all patients. Rate of fluid infusion was kept at 5 mL Kg^{-1} h^{-1}, avoiding colloids, calcium was administered to maintain ionized calcium levels at 1.2 mmol/L and sodium bicarbonate was infused to reach a pH greater than 7.30. Losses related to ascitis were corrected by the administration of 200 mL albumin 20%. Red blood cells packed (RBC's) were given in order to maintain hemoglobin concentration at 90 g/L. Fresh frozen plasma was only administered when the international normalized ratio (INR) resulted higher than 1.8 and active bleeding in the surgical field was detected. Platelets were given in order to maintain a platelet count above $50x10^9$ /L and 2 g of fibrinogen was administered when needed to maintain plasma fibrinogen levels >1 g/L. [10] No intraoperative cell salvage of blood was used during surgery. All patients were placed on a warm blanket of convection air (Warm-Touch, Mallinckrodt Medical). Liver allograft was preserved using University of Wisconsin solution. Prior to reperfusion of the graft, the liver was flushed with 1000 mL of Hartmann solution at 38 ºC in order to remove air and detritus through the entire inferior vena cava of the graft. Next, vascular stapler closed the distal end of the donor's vena cava.

The following data were analyzed: patient characteristics, biochemical and coagulation tests, presence of reperfusion syndrome, total fluid therapy, postoperative creatinin and outcome. Samples for biochemical and coagulation determinations were taken during different stages of the surgical procedure and 24 hours after the LT.

Variables and statistical analysis

The main variable of interest was the percentage of patients that do not require RBC's intraoperatively. The T-Student test or nonparametric Mann-Whitney U test were used to compare continuous variables depending on its distribution. Chi-square test was used to compare discontinuous variables. Statistical significance was set at P-value<0.05. Data are presented herein as an absolute number and percentage (%), mean and standard deviation or median and range.

Results

During the study period, 664 LT cases were performed. A total of 208 cases were excluded because of no or other antifibrinolitic therapy was applied or a different surgical technique was performed. For all excluded patients, 29% did not receive any blood product intraoperatively. As a result, both preservation of vena cava and tranexamic administration were fulfilled in 456 cases, in which 46.5% patients no blood product was used intraoperatively. When a propensity matching analysis for hemoglobin concentration was applied, considering values between 90 and 120 g/L, 190 patients resulted to be evaluated. Two groups were created according to the preoperative fibrinogen plasma level (cutting point based on a value of 2 g/L, which is the low normal value of our laboratory): the low fibrinogen group (61 cases) and the standard fibrinogen group (129 cases).

Patients' characteristics, surgical and outcome data are represented in table 1. INR, PTT and platelets were significantly different between groups in contrast to the hemoglobin concentration that remained similar in both groups. There were no differences in the length of surgery, cold ischemia, reperfusion syndrome, the lowest temperature and pH recorded and calcium values. Use of RBC's resulted significantly higher in the low fibrinogen group (median, 3 *vs.* 2). The number of patients with no blood product requirements was fewer in the low fibrinogen group (13% *vs.* 35%). However, intraoperative massive transfusion determined by more than 10 RBC's were similar in both groups. The use of fluids was similar in both groups (Table I).

Table I.—*Patient's characteristics, surgical procedure and outcome.*

	Low Fibrinogen (n=61)	Standard Fibrinogen (N.=129)	P value
Age (years)	54±11	55±9	0.79
Gender (male/female)	39/21	88/41	0.621
Child A/B/C	5/35/21	22/76/31	0.016
median [range]	9 [5 to 13]	8 [5 to 14]	0.004
MELD, UNOS modification (median [range])	11 [8 to 29]	10 [6 to 36]	0.230
Diagnose			0.574
Alcoholic Cirrhosis (%)	40 (65.5)	71 (55)	
C-Virus Cirrhosis (%)	4(6.5)	10 (7.75)	
Biliar Primary Cirrhosis (%)	—	4 (3)	
Hepatocelular carcinoma (%)	14 (23)	34 (26.5)	
Retransplantation (%)	3 (5)	10 (7.75)	
Preoperative			
Previous laparotomy (%)	14 (23)	34 (26)	0.720
Partial portal vein thrombosis (%)	5 (8)	13 (10)	0.641
Renal replacement therapy (%)	—	4 (3)	0.307
Sodium (mmol/L)	136±5	137±5	0.347
PTT ratio	1.49±0.37	1.23±0.27	<0.001
TP ratio	1.72±0.6	1.40±0.37	<0.001
Creatinine (mg/dL)	0.93±0.45	1±0.62	0.497
Hemoglobin (g/L)	104.2±8.6	105.6±8.3	0.286
Platelets count (10^3/mm^3)	73.5±52	104±65	<0.001
Surgical data			
Cold ischemia (minutes) (median [range])	396 [210 to 855]	405 [205 to 856]	0.827
Length of procedure (minutes)	372±73	381±76	0.432
Reperfusion syndrome (%)	28 (46)	53 (41)	0.638
pH value after reperfusion (median [range])	7.32 [7.16 to 7.48]	7.31 [7.13 to 7.44]	0.372
Calcium level after reperfusion (mmol/L) (median [range])	1.20 [0.94 to 1.50]	1.24 [0.9 to 1.7]	0.075
Lowest temperature after reperfusion (cent degree) (median [range])	35.2 [33.6 to 36.8]	35.5 [32.6 to 36.1]	0.085
RBC's Transfused units (median [range])	3 [0 to 10]	2 [0 to 27]	0.004
FFP Transfused units (median [range])	2 [0 to 11]	0 [0 to 34]	<0.001
Platelets units (median [range])	8 [0 to 40]	0 [0 to 25]	<0.001
Fluid therapy (ml) (median [range])	3760 [1000 to 5860]	4191 [1268 to 14565]	0.056
No RBC's requirements (%)	8 (13)	45 (35)	0.007
>6 RBC's transfused (%)	13 (21)	16 (12.5)	0.453
>10 RBC's transfused (%)	1 (1.6)	3 (2.4)	0.924
Postoperative data			
No RBC's requirements 1st 24 h. (%)	46 (75)	97 (75)	0.974
Creatinine mg/dl	1.55±0.93	1.3±0.63	0.267
Renal replacement therapy (%)	2 (3.3)	5 (4)	1
Reoperation (%)	2 (3.3)	6 (4.6)	0.488
Acute Retransplantation (%)	—	3 (2.3)	0.403
In hospital mortality (%)	6 (9.8)	16 (12.4)	0.809

Data expressed as: absolute number, (%); mean and standard deviation. PT: prothrombin time; PTT: activated partial thromboplastin time; RBCs: red blood cells; FFP: fresh frozen plasma.

Table II.—*Fibrinogen profile during liver transplantation procedure.*

	Low Fibrinogen (N.=61)	High Fibrinogen (N.=129)	P value
Preoperative fibrinogen g/L	1.63 [0.77 to 2]	3.4 [2.02 to 8.7]	<0.001
Hepatectomy fibrinogen g/L	1.58 [0.9 to 2.96]	2.95 [1.11 to 7.22]	<0.001
Anhepatic fibrinogen g/L	1.45 [0.9 to 3]	2.63 [1.2 to 7.2]	<0.001
Reperfusion fibrinogen g/L	1.15 [0.3 to 2.52]	2.21 [0.6 to 6.9]	<0.001
End-procedure fibrinogen g/L	1.32 [0.4 to 2.65]	2.24 [0.74 to 7]	<0.001
24 hour postransplantation fibrinogen g/L	3.02 [1.32 to 6.7]	3.85 [1.5 to 8.24]	<0.001

Data expressed as median [range].

In the low fibrinogen group, two grams of fibrinogen were administered to 20 patients, four grams to one patient, six grams to one patient and eight grams to two patients; while, two grams of fibrinogen were administered to six patients and four grams to one patient in the standard group.

Fibrinogen profile is shown in Table II. Although, plasma fibrinogen decrease occurred in both groups, the critical level of plasma fibrinogen for treatment (1 g/L) in the standard fibrinogen group was only reached after graft reperfusion in 7 cases (5.5%) *vs.* 24 cases (39%), p <0.001, in the low fibrinogen group.

Discussion

Our data suggest that preoperative plasma fibrinogen level of ≤2 g/L increases requirements for blood products during the surgical procedure of liver transplantation. A critical level of plasma fibrinogen (1g/L) was produced in LT at graft reperfusion in a significant percentage of patients when the preoperative plasma fibrinogen level was lower than 2 g/L. Use of RBC's resulted significantly higher in the low fibrinogen group, even though fibrinogen was corrected.

Preservation of vena cava and antifibrinolitic drugs, have proved usefulness in reducing RBC's requirements,[3, 11] these aspects were considered when cohorts were selected. We did not observe differences in the length of surgical procedure, reperfusion syndrome was also present in a similar percentage of patients from both groups and no differences were observed in terms of acidosis correction, plasma calcium administered and control of temperature. Therefore, differences in blood product requirements might be attributed solely to specific haemostatic and coagulation profiles that were observed through the surgical procedure. Patient's differences in relation to preoperative platelets could have influenced intraoperative bleeding; however, because of the high threshold for platelet transfusion determined by our protocol, most of patients in the low fibrinogen group received platelets. Fluid therapy regimen did not differ between groups indicating that hemodilution was not directly responsible of differences in bleeding and transfusion requirements.

We did not use intraoperative cell salvage because this technique has been stated in LT to be cost-effective only in massive transfusion [12] and also, it may increase blood loss.[13] In a series of patients with low transfusion rate, blood cell salvaged was administered in only 35% of cases.[14] Intraoperative massive transfusion determined by more than 10 RBC's was uncommon in our study, one patient in the low fibrinogen group and 3 patients in the standard fibrinogen group. This complication results from the confluence of several of these factors: a major surgical bleeding that occurs mostly at reperfusion of the graft, a severe hemodynamic disturbances and a significant fibrinolyis.[15-16] All these circumstances require an intensive treatment based on inotropic support, fluid therapy and blood components administration (red cells packed, plasma, fibrinogen and platelets), and antifibrinolytic drug therapy.[17] Patients with massive transfusion were out of the range in both fluid therapy and blood component usage, so that dilution coagulopathy, acidosis and in some cases mild hypothermia would occur, worsening both coagulopathy and hemodynamics, therefore preventive correction is fundamental.[17]

Coagulation profile during LT is mainly characterized by thrombocytopenia and hypofibrinogenemia.[18] In our study, a critical level of plasma fibrinogen below 1 g/L after graft reperfusion was observed seven times more in patients with preoperative low fibrinogen. At the graft reperfusion, the lowest value of platelets, hemoglobin and fibrinogen coexist with an increase of fibrinolysis and depletion of endogenous anticoagulant factors such as protein C and antithrombin III.[19] Tripodi *et al.*[20] observed that thrombin generation is limited in severe thrombocytopenia. However, they considered that normal levels of fibrinogen may facilitate platelet aggregation as well.

In surgical patients, it is proposed that fibrinogen should be corrected at a plasmatic level below 1.5-2 g/L.[21] Concerns about unwanted thrombotic events results in a major limitation of applying a corrective fibrinogen therapy. Whether normalizing plasmatic fibrinogen may have a clinical value to prevent bleeding still remains unclear and further studies are needed to support a preemptive fibrinogen correction.

Conclusions

To conclude, our data suggest that preoperative plasma fibrinogen level of ≤ 2 g/L increases requirements for blood products during the surgical procedure of liver transplantation.

Key messages

— A progressive plasma fibrinogen level decrease is produced in LT.

— A critical level of plasma fibrinogen (1g/L) was produced at graft reperfusion in a significant percentage of patients when the preoperative plasma fibrinogen level was lower than 2g/L.

— A critical level of plasma fibrinogen (1g/L) at graft reperfusion was associated to blood transfusion during LT.

— More research is urgently needed in order to determine the clinical value and safety of increasing the critical level of plasma fibrinogen in LT.

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