

Intraoperative Coagulation Changes in Children Undergoing Liver Transplantation

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Intraoperative changes in blood coagulation were observed in eight children undergoing liver transplantation using a simplified coagulation profile (prothrombin time [PT], activated partial thromboplastin time [aPTT], and platelet count) and thrombelastography. Preoperatively, PT and aPTT were moderately prolonged (1.5 times control), and platelet count was greater than 100,000/mm³ in all patients but one (91,000/mm³). During the preanhepatic and anhepatic stages, PT, aPTT, reaction time, and coagulation time improved toward normal values, but platelet count and maximum amplitude did not change. Significant changes in coagulation occurred on reperfusion of the grafted liver: PT, aPTT, reaction time, and coagulation time were prolonged, and platelet count, maximum amplitude, and clot formation rate decreased. A heparin effect, which did not require treatment, was seen on reperfusion in four patients. Fibrinolysis occurred during the operation in five patients and was treated with Epsilon-aminocaproic acid (EACA) in one. Blood coagulation improved slowly, and values were close to baseline 90 min after reperfusion. In general, the coagulation changes seen in these children are similar to those in adults but less severe, possibly because of the preponderance of cholestatic disease in children compared with the more common hepatocellular disease in adults. (Key words: Anesthesia; pediatric. Blood; coagulation. Surgery; liver transplantation.)

LIVER TRANSPLANTATION is characterized by perioperative coagulopathies, which often result in massive bleeding.¹ The coagulopathy of end-stage liver disease includes deficiency of all coagulation factors produced by the liver, thrombocytopenia, dysfibrinogenemia, and fibrinolysis. However, levels of fibrinogen and Factor VIII, which is produced by the vascular endothelium and the liver, are increased. In experimental animals² and in adults³ undergoing liver transplantation, dilutional coagulopathy occurs during the early phase of the operation. Further dysfunction in coagulation occurs during the anhepatic stage, and the fibrinolytic system can be activated by an imbalance between plasminogen and antiplasmin. The most severe change occurs on reperfusion of the grafted liver, caused by heparin activity from the heparin given during donor organ procurement or released from the donor hepatocytes, marked fibrinolysis, possibly in-

hibitors of coagulation released from the grafted liver, and a dilutional effect of the preservation solution.^{4,5} Blood coagulability improves slowly thereafter and returns toward normal by the end of operation if the grafted liver function is adequate.⁶

Similar changes appear to occur in children receiving liver transplants, but reports have been based on limited clinical studies.^{7,8} This study was designed to investigate intraoperative changes in the coagulation system of pediatric patients undergoing liver transplantation using a simplified coagulation profile and thrombelastography.

Methods

Eight consecutive children receiving liver transplants were included in the study. Ages ranged from 9 months to 7 yr (46 ± 27 months), and body weight from 6.6 to 20.8 kg (14.7 ± 4.4 kg). The preoperative diagnosis was biliary atresia in six patients, primary tyrosinemia in one, and primary nonfunction of the transplanted liver in one. Patients were prepared and anesthesia was maintained as described by Borland *et al.*⁸ Intravenous catheters (three or four) were inserted for infusion of crystalloids, colloids, and blood products. An intraarterial catheter (22-G) was inserted in a radial artery for blood pressure monitoring and blood sampling. In addition, a catheter was inserted in the right atrium or the pulmonary artery to monitor central venous pressure or pulmonary artery pressure. Monitored physiologic variables included electrocardiogram (ECG), esophageal temperature, serum levels of electrolytes and ionized calcium, blood glucose, arterial blood-gas tensions and acid-base state, and urine volume. Crystalloids were infused to maintain intravascular volume, packed red blood cells (RBC) to maintain hematocrit above 30 vol%, fresh frozen plasma (FFP) to equal the volume of transfused RBC, and platelet concentrates to keep platelet count above 100,000/mm³.

Blood samples (5 ml each) were obtained from the intraarterial catheter at the following times: after induction of anesthesia (baseline), 60 min after skin incision (I + 60), 30 min after removal of the liver (II + 30), 60 min into the anhepatic stage (II + 60), 5 min after reperfusion of the grafted liver (III + 5), 30 min after reperfusion (III + 30), and 90 min after reperfusion (III + 90). Prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count were measured⁹ and blood coagulability was tested by thrombelastography (Thrombelastograph®, Hellige, West Germany) in whole blood

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(0.36 ml).¹⁰ Measured thrombelastographic variables were reaction time (r , min), coagulation time ($r + k$, min), clot formation rate (α , °), maximum amplitude (MA, mm), amplitude 60 min after MA (A_{60} , mm), whole blood clot lysis index (WBCLI, $A_{60}/MA \cdot 100$, %), and fibrinolysis time (F , min) (fig. 1). Thrombelastography (TEG) assesses blood coagulability by measuring shear elasticity of fibrin strands formed between two highly polished metal surfaces. It evaluates all phases of coagulation including coagulation and fibrinolysis, and its variables are known to correlate well with clinical conditions.^{11,12} Activity of coagulation factors is demonstrated by reaction time and coagulation time, platelet function by maximum amplitude, fibrinogen activity by clot formation rate, and fibrinolytic activity by fibrinolysis time.

Two additional blood samples were tested by TEG 5 min after reperfusion of the grafted liver (III + 5), one treated with Epsilon-aminocaproic acid (EACA) (0.03 ml of 1% solution in 0.33 ml of blood) and one treated with protamine sulfate (0.03 ml of 0.01% protamine sulfate in 0.33 ml of blood) to determine the degree of fibrinolysis and heparin effect.

Data are reported as mean \pm SD; they were analyzed by analysis of variance of repeated measures (ANOVA), and specific differences were assessed with the Student-Newman-Keuls test. $P < 0.05$ was considered statistically significant.

Results

Patients received 85 ± 106 ml/kg of RBC (14–184 ml/kg), 122 ± 62 ml/kg of FFP (29–199 ml/kg), and 100 ± 51 ml/kg of crystalloid solution (30–172 ml/kg). Four children received platelet concentrates (10–24 ml/kg). Hematocrit was maintained above 30 vol% in most patients and was 41.4 ± 4.4 vol% at the end of surgery.

Intraoperative changes in their coagulation profiles are shown in table 1. Initial PT was $1.5 \times$ the laboratory control value (12 s), but it decreased during the operation, reaching its lowest values during the anhepatic stage ($1.15 \pm 0.11 \times$ control). PT increased immediately after reperfusion but was close to the baseline value at the end of the procedure. A similar change occurred in aPTT. Preoperative platelet count was higher than $100,000/\text{mm}^3$ in all patients but one, in whom it was $91,000/\text{mm}^3$. Decreases in platelet count occurred 5 min and 30 min after reperfusion, particularly in four children (55,000, 69,000, 93,000 and $100,000/\text{mm}^3$, respectively). Platelet concentrates were transfused in volumes of 10, 14, 24, and 24 ml/kg.

Intraoperative changes in blood coagulability are reflected in TEG variables (table 1). Initially, reaction time and coagulation time were slightly prolonged, but they returned to normal values during the preanhepatic and

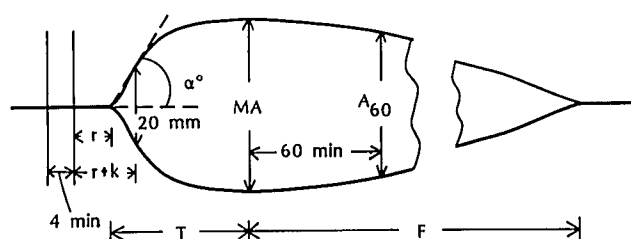


FIG. 1. Variables measured by thrombelastography and their normal values: r = reaction time (min); $r + k$ = coagulation time (min); T = time for maximum amplitude (min), α = clot formation rate (°); MA = maximum amplitude (mm); A_{60} = amplitude 60 min after maximum amplitude (mm); F = fibrinolysis time (min); and WBCLI = whole blood clot lysis index ($A_{60}/MA \cdot 100$, %). Reprinted from ANESTHESIOLOGY 66:766–773, 1987, with permission of the American Society of Anesthesiologists.

anhepatic stages. They were markedly prolonged 5 min after reperfusion of the grafted liver and then returned toward baseline values. Maximum amplitude and clot formation rate did not change significantly except 5 min after reperfusion (from 47.3 ± 7.9 to 27.3 ± 20.0 mm and 48.9 ± 8.0 to $22.5 \pm 17.7^\circ$, respectively). Five patients showed evidence of fibrinolysis, defined as either fibrinolysis time (F) of less than 180 min or whole blood clot lysis index (WBCLI) of less than 80%. Fibrinolysis time was less than 180 min in three children during the anhepatic stage or 5 min after reperfusion, and less than 60 min in one patient during the anhepatic stage and on reperfusion. In all patients fibrinolysis time was longer than 180 min at the end of the operation. WBCLI tended to decrease intraoperatively ($P = 0.1$) and increased to $92.1\% \pm 7.5\%$ toward the end of the operation.

TEG variables measured 5 min after reperfusion in a blood sample treated with EACA, in a blood sample treated with protamine sulfate, and in an untreated sample are shown in table 2 and figure 2. In only one patient were values in the untreated sample similar to those in blood treated with EACA or protamine sulfate. In four patients blood treated with protamine sulfate showed significant decreases in reaction time and coagulation time, but no patient was given protamine sulfate to counteract the heparin effect. In seven of eight patients the blood treated with EACA showed shortened reaction time and coagulation time, increased maximum amplitude and clot formation rate, and increased WBCLI.

Severe coagulopathy developed in a 7-yr-old boy (21 kg) with intrahepatic biliary atresia (fig. 1). Baseline coagulation profile of this patient was PT $3.1 \times$ control, aPTT $2.7 \times$ control, platelet count $91,000/\text{mm}^3$, and mildly prolonged reaction time and decreased maximum amplitude on TEG. An abrupt change was seen on reperfusion: PT $1.2 \times$ control; aPTT $1.9 \times$ control; reaction time 34 min; maximum amplitude 2 mm; and fibrinolysis

TABLE 1. Intraoperative Coagulation Changes in 8 Children Undergoing Liver Transplantation

Sampling time	aPTT (x control) (s)	PT (x control) (s)	Platelet Count (1,000/mm ³)	r (min)	r + k (min)	MA (mm)	Clot Formation Rate (α, °)	WBCL1 (%)
Normal value	12	24	150-250	6-8	10-12	50-70	45-60	>80
Baseline value	1.5 ± 0.65	1.5 ± 0.59	182 ± 88	9.6 ± 6.2	19.0 ± 14.6	46.9 ± 11.5	39.0 ± 18.0	84.6 ± 12.7
I + 60 min	1.38 ± 0.24	1.34 ± 0.35	178 ± 84	7.4 ± 1.5	12.8 ± 3.3	47.3 ± 12.3	44.0 ± 8.9	84.3 ± 8.1
II + 30 min	1.15 ± 0.11	1.1 ± 0.1*	172 ± 93	6.9 ± 1.9	11.9 ± 4	48.1 ± 9.4	47.4 ± 10.2	69.0 ± 30.2
II + 60 min	1.18 ± 0.13	1.14 ± 0.13*	172 ± 91	7.4 ± 2.8	11.9 ± 3.7	47.3 ± 7.9	48.9 ± 8.0	71.9 ± 25.9
III + 5 min	1.31 ± 0.16†	1.59 ± 0.25†	152 ± 93*†	22.4 ± 15.4*†	59.3 ± 40.9*†	27.3 ± 20.0*†	22.5 ± 17.7*†	70.5 ± 32.5
III + 30 min	1.35 ± 0.14†	1.49 ± 0.29†	154 ± 77*†	10.1 ± 2.4†	16.5 ± 4.2†	46.1 ± 9.7	39.4 ± 9.4†	92.4 ± 2.6†
III + 90 min	1.4 ± 0.24†	1.55 ± 0.32†	157 ± 63	9.2 ± 3.2	14.8 ± 5.2	49.9 ± 8.8	42.7 ± 8.3†	92.1 ± 7.5†

Values are mean ± SD.

* $P < 0.05$, compared with the corresponding preoperative values.

† $P < 0.05$, compared with the corresponding values at II + 60 min.

time 30 min. Comparison of TEG of blood samples treated with EACA or protamine sulfate and the untreated sample showed presence of fibrinolysis and heparin effect. Fibrinolysis was treated by iv infusion of a single dose of EACA (20 mg/kg), and the operation ended with a normal TEG. This child received 186 ml/kg of RBC, 190 ml/kg of FFP, 24 ml/kg of platelet concentrates, and 144 ml/kg of crystalloids.

Discussion

Six of the eight children in this study had cholestatic disease. However, two children (one with tyrosinemia and one with primary nonfunction of the grafted liver) had similar changes in coagulation to those with cholestatic disease, and they were not separated in the analysis. The number of patients in this study is relatively small, and further investigation is required encompassing all types of liver diseases in children.⁸

TABLE 2. Thrombelastographic Variables Measured 5 min after Reperfusion of the Grafted Liver in Blood Samples Without Treatment and Treated with EACA or Protamine Sulfate

Variable	Blood Without Treatment	Blood with EACA	Blood with Protamine Sulfate
Reaction time (min)	22.4 ± 15.4	13.4 ± 7.0*	16.0 ± 4.8†
Coagulation time (min)	59.3 ± 40.9	34.1 ± 34.8*	34.6 ± 30.1*
Maximum amplitude (mm)	27.3 ± 20.0	47.4 ± 11.8*	35.1 ± 12.6†
Clot formation rate (°)	30.3 ± 25.8	46.0 ± 18.3	46.6 ± 19.3
Whole blood clot lysis index (%)	70.5 ± 32.5	98.4 ± 1.6*	73.6 ± 30.1†

Values are mean ± SD.

* $P < 0.05$, compared with the corresponding values in blood samples without pharmacologic treatment.

† $P < 0.05$, compared with the corresponding values in blood samples treated with EACA.

The preoperative coagulopathy observed in this study appears to be associated with decreased hepatic synthesis of coagulation factors demonstrated by prolonged PT and aPTT and a slightly decreased platelet count. A complete coagulation profile including assays of coagulation factors might have been more informative, but these tests are not used routinely in pediatric liver transplantation. Similar findings were obtained in the assessment of blood coagulability by TEG. Reaction time (r) and coagulation time (r + K), which represent the time to formation of

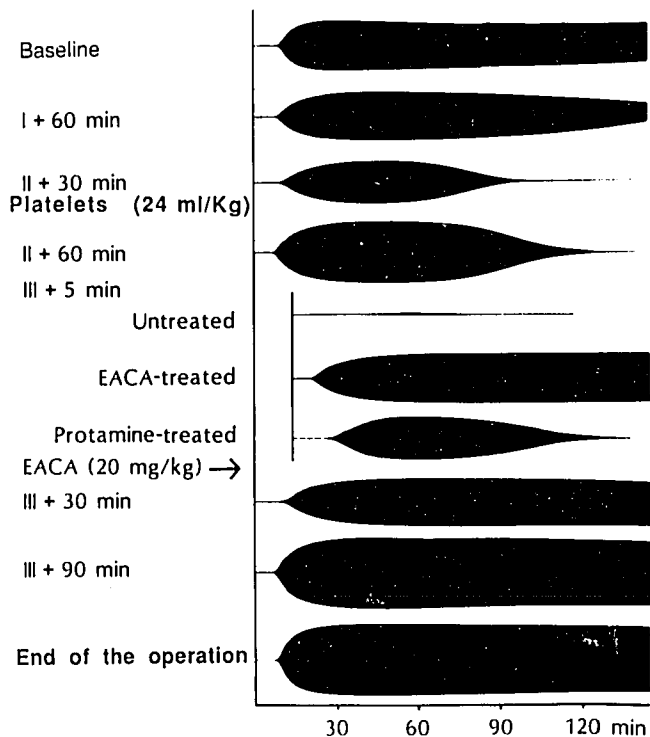


FIG. 2. Thrombelastographic patterns of a child given EACA (20 mg/kg) during liver transplantation. I + 60 = 60 min after skin incision; II + 30 = 30 min after hepatectomy; II + 60 = 60 min after hepatectomy; and III + 5, III + 30, and III + 90 = 5 min, 30 min, and 90 min after reperfusion of the grafted liver, respectively.

initial fibrin strands, were slightly prolonged. Platelet function, reflected by maximum amplitude (MA), was close to normal.

A gradual deterioration of coagulation is expected from a dilutional effect during the preanhepatic and anhepatic stages of the operation, but PT, aPTT, and TEG variables improved, possibly from replenishment of coagulation factors by FFP transfusion. In children who did not receive platelet concentrates, platelet count decreased from $208,000 \pm 82,000$ to $142,000 \pm 51,000/\text{mm}^3$ during infusion of 195.5 ml/kg of fluids. This decrease in platelet count is relatively less than observed in adults.³

Although deterioration in the coagulation profile was seen on reperfusion of the grafted liver in these children, the changes determined by TEG were even more dramatic. Reaction time and coagulation time increased to more than twice normal values, maximum amplitude and clot formation rate were half of normal values, and a heparin effect and fibrinolysis were observed. Pathologic coagulation also occurred on reperfusion but was less than is seen in adults.¹³ Heparin effect was seen in 50% of the children compared with 70% of adults. No heparin effect was seen 30 min after reperfusion, and no child required protamine sulfate. Fibrinolysis was detected in 62.5% of the children, compared with 82.5% of adults, and one child (12.5%) needed antifibrinolytic therapy compared with 21% of adults.¹³ In one child with severe fibrinolysis, administration of EACA after its antifibrinolytic effect was confirmed by TEG in a blood sample treated with EACA successfully treated fibrinolysis and oozing from the surgical field. EACA binds to plasminogen to accelerate conversion of plasminogen to plasmin, but the same binding inhibits the fibrinolytic process. Thrombotic complications may occur with antifibrinolytic therapy,¹⁴ but the antifibrinolytic agent alone does not promote clot formation: it prevents dissolution of clots that may form excessively or in an abnormal location.¹⁵ This limited study cannot rule out disseminated intravascular coagulation as a cause of fibrinolysis. Fibrinolysis seen during adult liver transplantation, however, has been suggested to be primary in origin, evidenced by marked increases in tissue plasminogen activators and fibrinogen degradation products,¹⁶ and selective decreases in Factor V and Factor VIII during active fibrinolysis.¹⁷ Furthermore, a recent study showed that a single dose (20 mg/kg) of EACA effectively treated fibrinolysis without thrombotic or hemorrhagic complications.¹³

In summary, intraoperative coagulopathy in children undergoing liver transplantation was similar to that in adults: poor preoperative coagulation state and severe coagulopathy on reperfusion. Nevertheless, these changes appear to be less severe than those in adults, possibly because of the preponderance of children with cholestatic

disease and their better hepatic reserve.¹ Also, the duration of the disease state may be relatively shorter, and the pediatric donor liver may have better hepatic function.

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