Coagulation Monitoring and Therapy in Liver Transplantation

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Coagulation Monitoring and Management

- Coagulation Monitoring and Management for OLT patients is not standardized from center to center.
- Evolution of surgical technique and coagulation management has decreased blood loss over the past decade.
- Still room for improvement in understanding and managing coagulation problems in ESLD.
Coagulation Monitoring

First line tests:
- Platelets count
- **Prothrombine time** (Extrinsic Pathway)
- **Activated Partial Thromboplastin Time** (Intrinsic Pathway)

Second line tests:
- **Trombin time**
- **Bleeding time**
- **Single Factor Plasmatic Activity**

Third line:
- **Thrombelastography (TEG)**
Clotting Pathway and Fibrinolytic System

Tests of Clotting Activation
(increased Thrombin generation)

- Thrombin-Antithrombin Complex
- Fibrinopeptides A and B
- Prothrombin Fragment F1 + 2
- Thrombin Generation
- Fibrin Monomers and Polymers

Tests for Fibrinolysis
(Hyperfibrinolytic Activity)

- Euglobulin Lysis Time
- Fibrin Degradation Products
- D-dimer
- Plasmin-α₂-Antiplasmin Complexes
Transfusion Therapy

- **RBCs:** Transfuse to maintain Hct 25-30%
- **FFP:** Transfuse to maintain INR at about 1.5
- **PLTs:** Transfuse to maintain PLT count > 50,000/mm³
- **Cryoprecipitate:** If FFP and PLT do not correct coagulopathy and fibrinogen levels are low (< 100 mg/ml)
No Blood Transfusion for OLT

Clinical Scenarios:
- Cross Match Problems: No blood available
- Patient Refusal of Blood Products: Jehovah Witness

Therapeutic Options:
- Cell Saver
- Acute Normovolemic Hemodilution
- PLT > 100,000
- Recombinant Human Erythropoietin

Blood Substitutes (oxygen carriers):
- Perfluorocarbons
- Hemoglobin substitutes
Thromboelastography (TEG)

- Comprehensive test of whole blood coagulation.
- Measurement of initial formation of fibrin strand (reaction time, r).
- Clot formation rate ($\alpha$) or speed at which solid clot forms.
- Progressive increase in amplitude to MA (Maximum Amplitude), maximum strength or stiffness of developed clot.
- Developed by Hartert in 1948, introduced by Kang (UPMC) to transplantation.
Thromboelastography (TEG)

- \( r \) = Reaction time = 10-14 min
- \( r + k \) = Coagulation time = 13-20 min
- \( \alpha \) = Clot formation rate = 53-67 °
- MA = Maximum amplitude = 59-68 mm
- \( A_{60} \) = Amplitude 60 min after MA
- \( A_{60}/MA \times 100 \) = Whole blood clot lysis index > 85%
- F = Whole blood clot lysis time > 300 min
Thromboelastography (TEG)
Coagulopathy Treatment During OLT

- Combines transfusion and pharmacological approaches.
- Complex nature of surgery and coagulopathy, known drug antifibrinolytic effect may not correlate with effective intraoperative blood loss.
Pharmacological Agents

- Aminocaproic Acid
- Tranexamic Acid
- Aprotinin
- DDAVP
- Conjugated estrogen
- Protamine
- Recombinant activated Factor VII (Novo Seven)
- Factor VIII + von Willebrand Factor (Humate-P)
Aminocaproic and Tranexamic Acid

- Stabilizes clot formation
  - Inhibits proteolytic activity of plasmin
  - Inhibits conversion of plasminogen to plasmin by plasminogen activators

- AMCA 6 times more potent than EACA
Aprotinin

- Serine protease inhibitor (trypsin, chymotrypsin, plasmin, tPA, urokinase plasminogen activator, kallikrein)
- Antifibrinolytic effect
- Protects glycoprotein IB receptors on PLT
Aprotinin in OLT

- Low dose continuous infusion without loading dose
- 200,000 KIU/hr vs NS
- FDP: Control (95% > 20 μ/ml), Aprotinin (53% > 20 μ/ml)

<table>
<thead>
<tr>
<th>Blood Products (units)</th>
<th>Aprotinin (n=21)</th>
<th>Control (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC</td>
<td>2.1 ± 2.0</td>
<td>3.0 ± 4.4</td>
<td>&lt; 0.36</td>
</tr>
<tr>
<td>FFP</td>
<td>3.6 ± 3.5</td>
<td>6.6 ± 6.1</td>
<td>&lt; 0.05 *</td>
</tr>
<tr>
<td>CS</td>
<td>2.5 ± 1.6</td>
<td>4.0 ± 5.0</td>
<td>&lt; 0.18</td>
</tr>
<tr>
<td>CRYO</td>
<td>5.7 ± 7.5</td>
<td>12.6 ± 12.8</td>
<td>&lt; 0.04 *</td>
</tr>
<tr>
<td>PLT</td>
<td>4.0 ± 7.3</td>
<td>5.0 ± 5.6</td>
<td>&lt; 0.6</td>
</tr>
</tbody>
</table>
Aprotinin in OLT
Lancet 2000; 335:1303-9

- **High Dose Aprotinin (n=46)**
  - 2 x 10^6 KIU Loading Dose
  - 1 x 10^6 KIU Infusion until 2 hr after reperfusion

- **Regular Dose Aprotinin (n=43)**
  - 2 x 10^6 KIU Loading Dose
  - 0.5 x 10^6 KIU Infusion until 2 hr after reperfusion

- **Placebo (n=48)**
Aprotinin in OLT
Lancet 2000; 335:1303-9

- Intraoperative Blood Loss
  - HD Aprotinin: 60 % reduction
  - RD Aprotinin: 44 % reduction

- Total RBC Transfusion (homologous + autologous)
  - HD Aprotinin: 37 % lower than placebo
  - RD Aprotinin: 20 % lower than placebo
Aprotinin in OLT
Lancet 2000; 335:1303-9

- Thrombotic Events
  - HD Aprotinin: 2 patients
  - RD Aprotinin: 0 patients
  - Placebo: 2 patients

- Mortality (30 day): no difference

- Conclusion: Significantly reduces blood-transfusion requirements and should be used routinely in patients without contraindications.
Desmopressin (DDAVP)
Seminars in liver disease 2002; 22(1); 83-96

- Improves coagulation in von Willenbrand’s disease, hemophilia A, renal failure
- Increases vWF Factor release from endothelial cells
- Increases F VIII activity (2-20 fold plasma increase)
- Antidiuretic effect (vasopressin analogue) with decreased pressor activity
Conjugated Estrogen

- OLT patients with TEG r-time > 15 minutes
- Randomized to receive Conjugated Estrogen (CE) 100 mg at the beginning of the procedure and after reperfusion.
- CE treated patients received less FFP, RBC and PLT
Coagulation Cascade Model of r VII a

TF-bearing cell

VIIa

TF

activated platelet

IXa VIIa

Xa Va

X

II

IX

VIIa TF

VIIIa Va IXa

Xa Va

II

VIII/vWF → VIIa

V → Va

XI → Xla

platelet

Xla

IX

Xla
rFVIIa May Improve Clotting Function in OLT as Measured by TEG
Liver Transplantation 2001; 7(6): C-18(72)

- 18 Patients randomized
- TEG assessed before and 15 minutes after rFVIIa administered
- Significant effect of rFVIIa on r-time, K-time, $\alpha$-angle, but not on MA.
### Percent Change in TEG Parameters

Liver Transplantation 2001; 7(6): C-18(72)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>( \Delta ) R-time Mean (Range)</th>
<th>( \Delta ) K-time Mean (Range)</th>
<th>( \Delta \alpha ) -angle Mean (Range)</th>
<th>( \Delta ) MA Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-17.9 (-6.3/26.7)</td>
<td>6.6 (-11.3/48.1)</td>
<td>3.1 (-16.9)</td>
<td>13.1 (0/36)</td>
</tr>
<tr>
<td>20 ( \mu/kg ) rFVIIa</td>
<td>-31.4 (-27.7/35.3)</td>
<td>-37.3 (0/-67.4)</td>
<td>12.9 (1.3/45.8)</td>
<td>9.3 (2.7/22.2)</td>
</tr>
<tr>
<td>40 ( \mu/kg ) rFVIIa</td>
<td>-21.1 (35.4/-49.3)</td>
<td>-4.5 (11.5/-22.5)</td>
<td>3.5 (-6.7/8.8)</td>
<td>18.5 (-5.0/109.3)</td>
</tr>
<tr>
<td>80 ( \mu/kg ) rFVIIa</td>
<td>-34.2 (-10.0/-49.1)</td>
<td>-3.1 (-20.0/31.6)</td>
<td>0.9 (-7.0/8.3)</td>
<td>4.2 (-5.9/36.1)</td>
</tr>
</tbody>
</table>
Hypercoagulation Work-up

- PT, PTT, INR, PLT
- Antithrombin III (AT III)
- Protein C, protein S
- Factor II
- Factor V Leiden
- MTHFR (methamine-tetra-hydrofolate-reductase): gene mutation marker for homocysteinemia
- Antiphospholipid/anticardiolipin protein (lupus anticoagulant)
Hypercoagulability Based on TEG

- Short r time < 10 mm
- Increased $\alpha$ angle (> 67°)
- Increased MA > 68 mm
Physiologic Inhibitors of the Coagulation Pathway:

- Antithrombin III
- Tissue Factor Pathway Inhibitor
- Activated Protein C
- Protein S
Antithrombin III

- AT III is synthesized in the liver and has a half time 60 h
- Plasma concentration is 3-5 μmol/l (~ 150 mg/l)
- The activity of AT III is measured in U/ml or %, normal 0.8 U/ml (80 %) to 1.2 U/ml (120 %)
- 1 ml FFP = 1 U AT III
Hereditary AT III Deficiency

- Associated with an increased risk for developing deep vein thrombosis or pulmonary embolism.
- Type I, quantitative deficiency: reduction to ~ 50 % of AT III plasma activity.
- Type II, qualitative deficiency: normal AT III concentration, but functional activity is reduced.
- AT III replacement to keep AT III level > 80 %.
Liver disease $\downarrow$ AT III without a hypercoagulable state ($\downarrow$ synthesis of procoagulant clotting factor).

Prophylactic AT III substitution prior to OLT showed no relevant clinical benefits.

Blood loss and transfusion requirements were not affected by AT III administration.
AT III Levels & DIC in OLT
Anesthesiology 89 (3AS) Supplement : 412, 1998

- 81% of patients (n=30) have < 80% AT III activity and 23% had DIC before surgery.
- DIC increasing to 50% at reperfusion and to 80% at 30 min after reperfusion.
- Decreases in AT III precede secondary fibrinolysis.

Fibrinolytic Tests: D-dimers, FDP, soluble fibrin monomer complexes
AT III Deficiency in Sepsis
Chest 104: 882-8, 1993

- AT III 90-120 U/kg body/ day for 5 days in patients with septic shock.
- Non significant better outcome in AT III group
- Duration of DIC was significant shorter.
Loading dose of 6000 IU, followed by a continuous IV infusion of 6000 IU/day for 4 days

AT III therapy no effect on mortality in sepsis

AT III associated with an increased risk of hemorrhage when administered with heparin.

Benefit of AT III in the subgroup of patients not receiving concomitant heparin.
DVT was found in 35 % patients with AT III and heparin prophylaxis.

DVT was diagnosed in 80 % of the patients treated with dextran 40.
Hypercoagulability

ILTS ELTA LICAGE Berlin 2001, C-5: 18

- 4 cases intravascular/intracardiac thrombosis:
  - Hypercoagulable TEG
  - Clotted blood sample
  - AT III < 60
  - No antifibrinolytic drugs were used

- Heparin small doses < 5000 units
- 500 U of AT III replacement
Pulmonary Thromboembolism During OLT: Possible association with antifibrinolytic drugs

**Case 1:**
Hepato-renal syndrome and HD
Before incision:
- 5 g EACA bolus + 1 g/h
During VVBP switch to:
- 2 million KIU aprotinin + 200,000 KIU/h
- Patient died

**Case 2:**
Sepsis and HD
- 2 million KIU aprotinin + 500,000 KIU/h
- Brain dead 2 days post-op
Pulmonary Thromboembolism During OLT: Possible association with antifibrinolytic drugs

Case 1:
Previous OLT, renal failure
- 2 million KIU aprotinin + 500,000 KIU/h
- Thrombectomy performed and OLT aborted

Case 2:
HD for hepato-renal syndrome
- 5 g EACA + 1g/h
During VVBP switch to
- 2 million KIU aprotinin + 250,000 KIU/h
- Survived OLT, never regained consciousness
Pulmonary Thromboembolism During OLT: Possible association with antifibrinolytic drugs

Case 1:
Ambulatory patient
No VVBP
- 1 million KIU aprotinin + 250,000 KIU/h
- Died in OR despite maximum resuscitation

Case 2:
Ambulatory patient
No VVBP
- 2 million KIU aprotinin + 500,000 KIU/h
- Died in ICU after complicated course
Aprotinin
Prohemostatic versus Prothrombotic effect

- Randomized, double-blind, placebo-controlled
- Coagulation: Fbg, APTT, PT, PLTs
- Fibrinolysis: tPA antigen and activity, plasminogen activator inhibitor activity and D-dimer
- TEG: r, $\alpha$ angle, MA.
Aprotinin
Prohemostatic versus Prothrombotic effect

- 2 million KIU at induction + 1 million before reperfusion (n=10)
- 2 million KIU at induction + 500,000 KIU/h (n=8)
- Placebo (n=9)
During anhepatic and postreperfusion, fibrinolytic activity (D-dimer and tPA antigen) was lower in aprotinin group compared with placebo.

Coagulation time (APTT and r time) were prolonged in aprotinin-treated patients compared with placebo.

No difference was seen in the incidence of perioperative thrombotic complication in the entire study population (n=137).
Pulmonary Thromboembolism During OLT: Possible association with antifibrinolytic drugs

- 7 cases intracardiac thrombosis
- 5 patients received EACA

Recommend:

- **NO** EACA and protamine during the dissection and anhepatic phase.
- Small doses of EACA after graft reperfusion are recommended.
- Transesophageal echocardiography useful in diagnosing and treatment monitoring
Case 1:
Thromboembolism after reperfusion

- 46 years, man, ESLD 2° to HCV and ETOH.
- Piggy-back technique, UW solution
- Cardiac arrest after reperfusion 2° to ↑K⁺:
  - Stage I K⁺ = 3.3 mmol/l and stage II K⁺ = 4 mmol/l
  - III + 30`: K⁺ = 9 mmol/l and III + 5`: K⁺ = 7 mmol/l
- CPR, cardioversion for VFib, epinephrine
- Heparin 2 x 5000 u
Case 2:
Intracardiac thrombus during dissection phase

- 59 years, woman, acute on chronic hepatic failure (PNC-A).
- Glasgow Coma Score 5,
- Mechanical ventilation
- Fluid overload with anasarca
- Renal failure with CVVH
Case 2:
Intracardiac thrombus during dissection phase

- PLTs 54 x 10^3 /mm^3
- PT 42 s
- INR 3.6
- APTT 38.6 s
- Short r time 2.1 mm (normal 10-14 mm)
- $\alpha$-angle of 65.5° (normal 53-67°)
- MA of 47.5 mm (normal 59-68 mm)

NO anticoagulant drugs were used for CVVH because of the coagulopathic status with severe epistaxis, which required tamponade one week before OLT.
Case 2:
Intracardiac thrombus during dissection phase

- 3 hour after incision
- BP ↓ from 110/55 to 95/45 and to 38 mmHg
- CVP ↓ from 21 to 5 mmHg
- ET-CO2 ↓ from 31 to 21 mmHg
- ABG sample clotted
- CVVH system clotted and failed
- TEE: free-floating thrombus in the RA
Case 2: Intracardiac thrombus during dissection phase

- Heparin 3000 u + 2000 u
- 1.1 mg of epinephrine was administrated + epinephrine infusion of 0.05 mcg/kg/min.
Case 2: Intracardiac thrombus during dissection phase

- When the hepatectomy was complete, TEE showed thrombus present in the RA and RV.
- Risk for migration into the PA upon reperfusion
- Hepatic vein cuff prepared for piggyback anastomosis was opened and a yankauer suction was passed through the IVC into the RA under TEE guidance to evacuate thrombus.
Case 2:
Intracardiac thrombus during dissection phase

- Protein C < 10 % (normal 70-140 %)
- Protein S 27 % (normal 60-145 %)
- AT III 27 % (normal 80-120 %)