Bleeding and Management of Coagulopathy

Jerrold H. Levy, MD, FAHA
Professor of Anesthesiology
Deputy Chair for Research
Emory University School of Medicine
Director, Cardiothoracic Anesthesiology
CT Anesthesiology and Critical Care
Emory Healthcare
Atlanta, Georgia
Chinese Character of Blood

Blood Drainage after Surgery

Sacrifice

Alter
COMPONENTS OF HEMOSTASIS

- Vasculature
- Coagulation proteins
- Platelets
Hemostasis

Subendothelial matrix

Platelets

Hemostatic plug

Fibrin

Endothelial cell

RBC

WBC
CLOT FORMATION

- Platelet
- Red Blood Cell
- Fibrin
VASCULAR ENDOTHELIUM

DIC

- Triggered by TF/endothelial injury
- Produces fibrin deposition in microvasculature and MOS dysfunction
- Path: Microangiopathic hemolytic anemia
- Lab: ↓ platelets, ↓ fibrinogen, ↑ PT, ↑ PTT, ↑ D-dimers, ↓ ATIII
LIMITATIONS TO TRANSFUSIONS AND RISKS

- Transfusions associated with adverse outcomes
- Most studies evaluate RBC transfusions
- Transfusions are associated with both risks/costs; availability is issue too
- What is the efficacy of transfusions in treating surgical bleeding or reversing coagulopathy?
MINIMUM FACTOR LEVELS FOR HEMOSTASIS

• "Spontaneous" Bleeding: 5-20%
• Minimum Conc for Hemostasis for Major Surgery: 20-30%
• Fibrinogen: ~100 mg/dl (??) but normal levels 200-350 mg/dl

PLATELET FUNCTION EVALUATION

- Platelet count
- Bleeding time
- Aggregation
- TEG/SonoClot
- Platelet function assays
- Experimental
PROHEMOSTATIC AGENTS
PHARMACOLOGIC PROHEMOSTATIC AGENTS

- Aprotinin
- Lysine analogs
- Protamine
- DDAVP (desmopressin)
- Recombinant Factor VIIa (rVIIa, NovoSeven)
- Protein concentrates, fibrinogen
- Fibrin glue/topical thrombin
LYSINE ANALOGS: Epsilon aminocaproic acid and tranexamic acid
EACA/Tranexamic acid

- Often small numbers, variable design, ?Tx criteria, ?Factor reduction
- Most data is TA, NOT EACA
- Doses of TA range from 2 g to 25 g
- Most EACA/TA studies with lower risk patients
- Meta analyses need to be cautiously interpreted
- EACA removed from many European markets

- 100 pts in a D, PC, R study to receive EACA (100 mg/kg before incision, 1 g/hour infusion until chest closure, 10 g in CPB circuit) vs placebo.
- Postop CT drainage EACA 649 (261) vs 940 (626) mL; p=0.003).
- No differences RBC Tx: EACA 24% v 18% placebo, p=0.62 or units Tx (EACA 2.2 (0.8) v 1.9 (0.8 U), p=0.29.
- EACA did not reduce risk of RBC Tx compared with placebo (odds ratio: 1.2, 95% confidence interval; 0.4 to 3.2, p=0.63).
- EACA reduced postop CT drainage volume by 30% but did not reduce need for allogeneic Tx.
SAFETY DATA WITH LYSINE ANALOGUES
SEIZURES/TRANEXAMIC ACID

- Yeh HM: Convulsions and refractory ventricular fibrillation after intrathecal injection of a massive dose of TA. Anesthesiology 2003; 98: 270-2
- Furtmuller R: TA, a widely used antifibrinolytic agent, causes convulsions by a GABA antagonistic effect. J Pharmacol Exp Ther 2002; 301: 168-73
PROTAMINE

• Basic polypeptide isolated from salmon sperm
• 70% arginine, reverses unfractionated heparin not LMWH
• Heparin rebound can occur
• Produces ADRs
• No alternatives available
Excess protamine causes hemostatic dysfunction

Mochizuki: Protamine reversal of heparin affects platelet aggregation and ACT after CPB. Anesth Analg 1998; 87:781-785
ANAPHYLAXIS TO PROTAMINE

• All patients: 0.06% (1/1500)
• NPH diabetics: 0.6-2% (1/50-1/160)

Levy JH: Anesth Analg 1986; 65:739
Levy JH: JTCS 1989; 98:200
PROTAMINE REACTIONS
PATHOPHYSIOLOGY

• IgE antibodies
• IgG antibodies
• Complement activation
• Direct/indirect effects
Desmopressin (DDAVP)
Summary: DDAVP Rx on surgical bleeding with inherited coagulation disorders

- Data includes small numbers, mostly retrospective analyses
- Data includes multimodal approaches
- Antifibrinolytics are used concomitantly and other factor concentrates
- Bleeding depends on types of surgical procedure; superficial vs major vascular/cardiac/neuro
- Monitoring effects, especially with platelet function tests, is limited

- Meta-analysis of all randomized, controlled trials of aprotinin, lysine analogues and desmopressin).
- 72 trials (8409 pts) were included.
- Aprotinin decreased mortality almost two-fold
- Both decreased the frequency of surgical re-exploration and allogeneic blood Tx.
- Desmopressin resulted in a 2.4-fold increase in the risk of MI, a small decrease in periop blood loss, but NO beneficial effects on other clinical outcomes.
Recombinant Factor VIIa (rFVIIa)
rVIIa (NovoSeven®)
Mechanism of Action

• NovoSeven® is human rFVIIa
• rFVIIa increases TF occupancy
• rFVIIa in pharmacological doses binds to activated platelets
• rFVIIa provides FX activation independent of Tissue Factor (TF)
• Improves platelet function
REPORTS OF rFVIIa: Cardiac Surgery


- Critical safety data obtained from 13 Novo sponsored clinical trials of rFVIIa in patients with coagulopathy due to anticoagulant therapy, cirrhosis, or severe traumatic injury.
- Thrombotic AEs were reported for 5.3% (23/430) of placebo and 6.0% (45/748) of active treatment.
- No significant differences was found between placebo-treated and rFVIIa-treated patients for thrombotic AEs, either on an individual trial basis or for these trial populations combined (p = 0.57).
Rescue Therapy with rVIIa in the Perioperative Setting: Off label

- Severe (1 L/hr) or life-threatening (CNS) bleeding without surgical source of bleeding
- Marginal response to routine hemostatic therapy (i.e., platelets, FFP, cryo, DDAVP)
- Judicious use with CV disease, DIC or ongoing activation (CPB)
- Consider lower dose (30 mcg/kg)
- Patients with multiple antibodies and platelets/factors not available

Goodnough LT: Transfusion 2004;44(9):1325-31
Fibrinogen
Hypofibrinogenemia

- Fibrinogen is an acute phase reactant; levels increase as an inflammatory response.
- Normal fibrinogen levels = 200-400 mg/dl; however most algorithms recommend Tx @ 100 mg/dl.
- Fibrinogen corrects TEG, RoTEM abnormalities, and increase clot strength.
- In US, cryoprecipitate is used: CRYO contains also vWF and FXIII.
- Elsewhere fibrinogen concentrates are used.
Cryoprecipitate: proteins per bag

• FVIII, IU/bag: 80 – 100
• vWF, IU/bag: 80 – 100
• Fibrinogen mg/bag: 150 – 250
• FXIII, IU/bag: 50 – 100
• Fibronectin, mg/bag: 50 – 60
Factor XIII
FXIII

- FXIII belongs to the family of transglutaminases, thiol enzymes that catalyze covalent crosslinking of proteins in tissues and involved in hemostasis.
- FXIII acts as the final enzyme in coagulation cascade; catalyzes cross-linking of fibrin molecules converting the primary blood clot into a stable form.
- FXIII crosslinks other substrates such as alpha-2-antiplasmin, thus controlling the rate of fibrinolysis, and some extracellular matrix proteins such as fibronectin and collagen, thus anchoring the clot into the site of injury.
FXIII activity (%)

TOPICAL HEMOSTATIC AGENTS

• Gelatin sponge: Gelfoam®, purified pork skin gelatin (Jello)
• Oxidized regenerated cellulose: Surgicel or Oxycel, from alpha-cellulose (plant-based)-in knit or microfibrillar form
• Microfibrillar collagen: Avitene ®- collagen derived from bovine skin
• Topical thrombin: bovine derived, human, and human recombinant (RECOTHROM™)
• Fibrin sealants: Tisseal/Crosseal (human fibrinogen, thrombin, aprotinin)
Treating Bleeding (1)

- Check ACT after protamine; AVOID excess protamine - Inc ACT may be low platelets
- Send fibrinogen and platelet count
- If PTT elevated, protamine ≤ 25 mg
- If still bleeding, consider platelets but check fibrinogen - Fibrinogen (cryo) corrects platelet dysfunction
- ?DDAVP; but ~Vasopressin?
Treating Bleeding (2)

- Treat anemia; may contribute to bleeding
- If marginal response to routine hemostatic therapy (i.e., platelets, FFP, cryo, DDAVP) consider OFF LABEL use of rFVIIa
- Restart antifibrinolytics
- With massive bleeding, initiate massive transfusion protocol
## Massive Transfusion Protocol for Cardiac Surgery Patients

<table>
<thead>
<tr>
<th>Pack</th>
<th>RBCs</th>
<th>FFP</th>
<th>PLTs</th>
<th>Cryo</th>
<th>rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4U</td>
<td>4U</td>
<td>1 AP</td>
<td>10U</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 mg</td>
</tr>
<tr>
<td>3</td>
<td>4U</td>
<td>4U</td>
<td>1 AP</td>
<td>10U</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4U</td>
<td>4U</td>
<td>1 AP</td>
<td>10U</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 mg</td>
</tr>
</tbody>
</table>
Thromboelastography recordings obtained with the ROTEM(R) device after the addition of rFVIIa and/or fibrinogen in the presence of tissue type plasminogen activator in volunteer plasma.

Increasing use of non reversible hemostatic inhibitors = bleeding in surgical/trauma patients

- IV antithrombins
- Platelet inhibitors (Clopidogrel, Prasugrel)
- LMWHs, pentasaccharide (Fondaparinux), other Xa inhibitors, and new agents
- All of the above
NOVEL ANTICOAGULANTS

- Direct thrombin inhibitors: r-hirudin (Refludan, Desirudin)
- Oral Xa inhibitors (rivaroxaban, apixiban)
- Oral thrombin inhibitors: dabegatran.
BleedingWeb.com