Anticoagulant to Procoagulant Therapies: Making Sense of the Coagulation Cocktails

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COMPONENTS OF HEMOSTASIS

• Vasculature
• Coagulation proteins
• Platelets

CLOT FORMATION
DIC

- Triggered by TF/endothelial injury
- Produces fibrin deposition in microvasculature and MOS dysfunction
- Path: Microangiopathic hemolytic anemia
- Lab: platelets, fibrinogen, PT, PTT, D-dimer, ATIII

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

- IV antithrombins
- Platelet inhibitors (Clopidogrel, Prasugrel)
- LMWHs, fondaparinux, other Xa inhibitors (rivaroxaban, apixiban), dabigatran
- All of the above

NOVEL ANTICOAGULANTS

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

LEVY IH: Novel anticoagulants: implications in the perioperative setting. Anesthesiology 2010
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


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
SAFETY DATA WITH LYSINE ANALOGUES

CRASH2: Lancet Epub, 2010

- 20,211 trauma patients randomized and treated ≤ 8 hrs of injury: 2 g tranexamic acid (TxA) or placebo
- In hospital mortality ≤ 4 weeks primary outcome: vascular occlusive events, transfusions, or surgical interventions were secondary outcomes
- All cause mortality = 14.5% TxA (1,463/10,060) vs 16% placebo (1,613/10,067) p=0.0035
- Bleeding related mortality reduced 4.9% vs 5.7% without increases in fatal or nonfatal vascular occlusive events
- No differences in transfusion

SEIZURES/TRANEXAMIC ACID

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

GABA

PROTAMINE
**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**

![Graph showing ACT (sec) vs PROTAMINE (mcg/ml)]

**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: JTCS1989; 98:200

**PROTAMINE REACTIONS PATHOPHYSIOLOGY**
- IgE antibodies
- IgG antibodies
- Complement activation
- Direct/indirect effects

**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

**Desmopressin (DDAVP)**

- 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 allogenic 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 rVIIa: Cardiac Surgery


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

- 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 increases clot strength.
- In US, cryoprecipitate is used: CRYO contains vWF and FXIII.
- Elsewhere, fibrinogen concentrates are used.

Hypofibrinogenemia

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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 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 the 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>
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<th>Pack</th>
<th>RBCs</th>
<th>FFP</th>
<th>PLTs</th>
<th>Cryo</th>
<th>rFVIIa</th>
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