Bleeding, Clotting and Finding the Balance: Implications for the CRNA

Aaron Ostrowski, CRNA, MSN
University of Pittsburgh Nurse Anesthesia Program

The Big Picture
- Insult to vessel, big or small
  - Trauma (shearing) or surgery (sharp)
- Clot forms: Hemostasis
  - Two major clotting factors: What are they?
    - Thrombin (IIa) and Fibrin (Ia)
- Clot dissolves: Fibrinolysis
  - One major player: What is it?
    - Plasmin

Role Players
- Platelets: major contributors
- Other clotting factors:
  - Intrinsic and Extrinsic pathways, classically
  - Now conceptualized as components of a coordinated, cell-based process
- Let’s look into this...

The Normal State of Things
- Endothelial cells control vascular tone:
  - Nitric oxide: vasodilator and antiplatelet agent
  - Endothelin: vasoconstrictor
- Active endogenous anticoagulants are circulating

Vascular Spasm
- Reflex
  - Immediately active
    - Lasts 20 to 30 minutes
  - Diminished by sharp-edged wounds
  - Small vessels from 30 to 50 microns
- When spasm isn’t enough...

Platelet Plug and the Coagulation Cascade
Platelets

- Vessel wall damage exposes collagen under the endothelium
  - Tissue Factor (III) is exposed with this damage, changes shape, and sensitizes platelets
  - A sensitized platelet morphs from a smooth, rounded shape into an irregular, tentacled coagulation factory.

The Classical View

Extrinsic Pathway

- Also called the Tissue Factor Pathway
- Circulating FVII contacts the exposed Tissue Factor (III) from the damaged endothelium
- FVIIa activates FX, known as “tenase”
  - FX then combines with FV
  - FXa + FVa = Mom & Pop thrombin production, aka "prothrombinase"^2
    - Soon to be bought out by a Big Box platelet producer
Roles of Thrombin

- Transform fibrinogen to fibrin
- Liberates vWF from FVIII
- Activates platelets at the site of injury
  - A potent positive feedback cycle
- Activates FV and FX for thrombin burst
- Activates Factor XI of Intrinsic Pathway
- Activates FXIII for clot stabilization

Intrinsic Pathway

- In vivo, not relevant to the initiation of a clot

Updated Concept: Initiation, Acceleration, Control, and Lyses

- Initiation: Endothelial damage followed by platelet plug formation
- Acceleration: Coagulation factor and further cellular activation
- Control: Feedback mechanisms activated
- Lyses: Clot breakdown and initiation of healing

Initiation and Acceleration

- Damage occurs to endothelium
- Tissue Factor released, attracts Factor VII
  - vWF released, bridges collagen and platelets via the GPIb receptor
  - Attracts other platelets, exposes GPIIb-IIIa receptor, other recruited platelets are interconnected bridges of soluble fibrin
- Platelets release their contents
  - Greater than 90 procoagulant substances
Control: Feedback to Endothelium

- Factor XIII stabilizes the clot
  - From soluble fibrin to insoluble fibrin
- Thrombin presence triggers endothelial thrombomodulin release, modifies thrombin
  - Proteins S and C counter Factors V and VII production in anticoagulant effect
- Intact neighboring cells carry a platelet-repelling charge
  - Limits the spread of the clot

Fibrinolysis: Clot Breakdown

- Plasminogen is incorporated into the clot during clot formation
- tPA: tissue plasminogen activator oozes from the surrounding intact endothelial tissue to initiate fibrinolysis
- Endogenous lysine binds to its receptor on plasminogen to convert it to plasmin

Coagulopathy

- Uncontrolled bleeding
  - marked by a consumption or dilution of coagulation factors
  - a loss of coagulation effect
- Associated with hypothermia, acidosis
  - Two other components of the "lethal triad"
- Early and late phases

Early Coagulopathy: ACoTS

- Acute Coagulopathy of Trauma-Shock
  - Sum of injury severity, blood loss, factor depletion, fibrinolysis, hypothermia (T<33 C), acidosis (pH<7.1) and the patient's intrinsic variable response
- ~25% of trauma patients present with a detectable coagulopathy
  - Direct activation of thrombomodulin-Protein C pathway by trauma to the body
  - Associated with a poor outcome
Late Coagulopathy

- More familiar version associated with dilution
- Massive bleeding
  - One blood volume in less than 24 hrs.
  - Loss of half of blood volume in three hours
- Blood product administration is hazardous
  - Increased mortality
  - Major adverse cardiac and noncardiac outcomes

Task Force for Advanced Bleeding Care in Trauma

- Convened in 2005 to 2006
- A group of European professional societies
- Critical survey of published literature with consensus agreement among the societies
- Formulated recommendations based on their findings...

Targeted Blood Pressure (2C)

- SBP of 80 to 100 mm Hg
  - Until major bleeding stopped in patients without brain injury
  - MAP of 80 mmHg recommended in TBI
- Increased blood pressure associated with increased hydrostatic pressure

Fluid Management (2C)

- Suggest crystalloids initially
- Colloids within prescribed limits
  - Studies are equivocal but suggest limits of 30 cc/kg
  - 3% Saline better than NS in increased ICP

Management of Bleeding, and Coagulation (1C)

- Target Hgb 7 to 9 g/dl
  - Rheological effect of RBCs may marginalize the platelets in the vessel
- FFP for coags > 1.5 times control
  - Dosed 10 to 15 cc/kg
  - Problems include overload, ABO, TRALI
- Platelets to maintain platelet count > 50K
  - A 4 to 8 pool or one apheresis pack

Packed Red Blood Cells

- Preserved in CPDA or “Additive Solution”
  - CPDA: Hct 70-75%, TV 275 ml, 35 day shelf life
  - Additive: Hct 60%, TV 350 ml, less citrate, 42 day shelf life, 75% fewer microaggregates
- One unit raises hgb 1g/dl and hct 3%
- With known ABO and Rh alone in naive pt.
  - 99.8% likelihood of a compatible transfusion
**Fresh Frozen Plasma**

- One unit is the plasma from one donated unit of whole blood
  - Contains preservative: CPDA or AS
  - Frozen quickly to preserve FV and FVIII
  - Must be ABO compatible, Rh not a factor
  - Dosing is 10 to 15 cc/kg, usually 4 units to replenish clotting factors adequately
  - 1 unit of FFP increases most factors ~2.5%

**Platelets**

- Dose is 1 unit/10 kg of body weight
  - Generally a 6 pool of platelets
  - Raises the platelet count 5 to 10 K/mcl
  - Four hour expiration
  - ABO compatibility not as critical
  - Very few RBC's and about 60 cc's of plasma in platelet pools

**Cryoprecipitate**

- A precipitate that remains when FFP is thawed slowly at 4°C.
  - One unit cryo is the yield from one unit of FFP
  - No ABO compatibility issues
  - Concentrated source of FVIII, vWF, FXIII, fibronectin and fibrinogen
  - Hypofibrinogenemia is less than 100 mg/dl
  - 6 pack of cryo raises fibrinogen by 45 mg/dl

**Transfusion Ratios**

- Low ratio is FFP to PRBC less than 1:4
  - Medium ratio is FFP to PRBC 1:4 to 1:2
  - High ratio is greater than 1 unit of FFP for every 2 units of PRBC
  - Has shown decreased rates of complication in massive transfusions after combat injuries
  - FFP to PRBC to Platelet of 1:1:1 with minimal crystalloid resuscitation

**Transfusion Practices**

- Transfusion with all components of whole blood in preserved form does not produce a whole blood equivalent
  - 1FFP+1PRBC+1PLT = Hct of 29%
  - Total volume of 660cc, platelets of 88K, and coagulation activity 65% of whole blood
  - Whole blood Hct is 38 to 50%, Plts 150 to 400K, and 100% of coag factors

**Tranexamic Acid:**

- Studies on surgical patients have used wide ranges of dosing
  - Loading doses: 2.5 to 100 mg/kg
  - Infusion doses: 0.25 to 4 mg/kg/hr
  - No benefit between high and low dosing
  - Bolus of 10 mg/kg and infusion of 1 mg/kg/hr provides sufficient plasma levels for antifibrinolysis
CRASH-2

- Randomized over 20,000 trauma patients
  - 274 hospitals in 40 countries
  - First patient enrolled in May, 2005
- Bolused with TA 1 gm over 10 mins and infused with TA 1 gm over 8 hours.
- TA reduces the risk of death from hemorrhage
  - No apparent increase in fatal or nonfatal vascular occlusive events
  - All-cause mortality was significantly reduced with tranexamic acid

References: