Bleeding, Coagulopathy, and Thrombosis in the Injured Patient

June 7, 2008

Kristan Staudenmayer, MD
Trauma Fellow UCSF/SFGH
Trauma deaths

Coagulopathy is Multi-factorial

Pre-injury Coagulopathy

Injury

Resuscitation

Bleeding Diatheses, Medications, other acquired coagulopathies

Coagulopathy Of Trauma

The Bloody Vicious Triad

Coagulopathy
Pre-Injury Coagulopathy

- Congenital and Acquired Coagulopathies are common

- Examples:
  - The number of people in the U.S. on warfarin is estimated at ~3 million
  - Most common congenital coagulopathy, von Wildebrand disease, in 1% of the population
Coagulopathy in Trauma

Coagulopathy of Trauma

- 3-4x increased mortality
- 8x higher mortality within 24 hours
- Higher incidence MOF
- Increased transfusion requirements

The Vicious Bloody Triad

Severe Trauma → Bleeding → Tissue Hypoxia → Acidosis
Severe Trauma → Bleeding → Fluid Replacement → Dilution
Severe Trauma → Bleeding → RBC Transfusion → Hypothermia
Management of Coagulopathies: The Hemostatic Toolkit
Hemostatic Tool-Kit

- FFP
- Platelets
- Cryoprecipitate
- Prothrombin Complex Concentrate
- Recombinant Factor VIIa
- Antifibrinolytics
- Desmopressin
Hemostatic Tool-Kit

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Cryoprecipitate

Contents: VIII, vWF, XIII, Fibrinogen
Pooled unit (bag) of 5-10 U

Concentration: Variable from site to site:
SFGH → 1 bag F’gen 750 mg, VIII 400 IU
May contain as low as 350 mg F’gen per bag

Treatment threshold:
Hypofibrinogemia <100mg/dL

Therapeutic Effect:
3 g (4 bags) increase F’gen ~1 g/l in adults
Prothrombomin Complex Concentrate (PCC)

- **Bebulin**® - II, VII (low), IX, X
- **Prothromplex**® - II, VII, IX, X, Prot C, AT

- Acute reversal of bleeding due to deficiency in vitamin K dependent coagulation factors

- **PCC vs. FFP**
  - FFP requires pretransfusion evaluation
  - FFP thawing may take 30-60 minutes
  - FFP volumes often exceed 1000mL
  - FFP often inadequate for reversing markedly elevated INRs
## Prothrombin Complex

### Dosing:

<table>
<thead>
<tr>
<th>Dose (IU)</th>
<th>Desired Increase (%)</th>
<th>In x 1.2 x BW (kg) Factors</th>
</tr>
</thead>
</table>

- 2,400 U (4 vials) increase factors ~30% in adults
Recombinant Factor VIIa

- Hemostatic agent
- Acts at the site of injury
- Enhance thrombin generation, leading to a stable fibrin clot

Figure 1: A cell-based model of coagulation (see text for further explanation).
Recombinant Factor VIIa

- Recombinant factor VIIa
  - Initially used in:
    - Hemophiliacs
    - Liver disease
    - Cardiac surgery
- In 1999, case report of use of factor VIIa to control bleeding in a trauma patient
- Has been shown to decrease transfusion requirements
- Expensive: $7,000 per dose

Recombinant Factor VIIa

**Other information**

- Must have platelets and fibrinogen to work
  - Fibrinogen > (0.5-) 1 g/l
  - Platelets > 50,000/mm³
- Acidosis minimizes effectiveness (pH > 7.2)
- Exact dose still under investigation → 80-90 mcg/kg
- Short half-life (2 hours)
Desmopressin (DDVAP)

Dosage: 0.3 mcg/kg BW over 30 min

- VIII, vWF increase within 30-60 min (3-5 x baseline), effect lasts 8-12 hours
- q 12-24 hours
- Tachyphylaxis

Antifibrinolytics in Trauma

Aprotinin
- Load 2 Mio kIU, Maint 0.5 Mio/h

ε-Aminocaproic Acid
- Load -150 mg/kg, Maint -15 mg/kg/h

Tranexamic Acid
- Load 1 g, Maint 120 mg/h for 8h [CRASH-2]

... There is insufficient evidence from the 2 randomized controlled trials of antifibrinolytic agents in trauma to either support or refute a clinically important treatment effect. ...

But in Reality...
Management of Coagulopathy

Pre-injury Coagulopathy

Bleeding Diatheses, Medications, other acquired coagulopathies

Coagulopathy Of Trauma

The Bloody Vicious Triad

Injury

Resuscitation

Coagulopathy

SCHOOL OF MEDICINE • UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Management of Specific Coagulopathies:

Acquired coagulopathies
Anti-Platelet Agents

- Antiplatelet agents
  - Inhibitors of platelet activation
    - Aspirin: Inhibits cyclo-oxygenase pathway and TXA formation
    - Thienopyridines (Plavix aka clopidogrel): inhibits ADP pathway
  - Inhibitors of platelet aggregation
    - GPIIb/IIIa antagonists
Anti-Platelet Agents

- All have permanent effect on platelets and therefore will have an effect x 7-10 days

- Dual antiplatelet therapy (ASA/Plavix) of benefit in multiple diseases
  - MI
  - Coronary artery stents
  - CVA
Anti-Platelet Agents

- **In vivo:**
  - No proven in vivo reversal for anti-platelet therapy

- **In vitro**
  - Transfusion of 20% platelets can reverse platelet inhibition
  - rVIIa can reverse impact of antiplatelet therapy on thrombin generation
Vitamin K Antagonists

- Common Types
  - Warfarin: half-life 5 to 45 hours
  - Superwarfarins (rat poison): half-life weeks to months
Vitamin K Antagonists

Reversal can be achieved in 3 ways:

1. Direct competition with vitamin K
   - Will not be effective in liver failure
   - Will take 12-24 hours to work

2. Replacement of coagulation factors
   - FFP or PCC

3. Bypassing the central part of the coagulation cascade with rVIIa.
Vitamin K Antagonists

ACCP guidelines recommendations:

1. Serious bleeding:
   - Vitamin K (10 mg by slow IV infusion) plus
   - FFP or PCC

2. Life-threatening bleeding:
   - Vitamin K (10 mg by slow IV infusion) plus
   - PCC and/or rVIIa

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. Chest 126 (3)S, 2004
Liver Failure

- Multiple hemostatic defects
  1. Low coagulation factors
  2. Low fibrinogen
  3. Thrombocytopenia
  4. Platelet dysfunction due to circulating inhibitors
  5. Decreased clearance of fibrinolytic enzymes
Liver Failure

- Replacement of missing factors
  - FFP. Large volumes may be required
  - Cryoprecipitate may be required if fibrinogen <100 mg/dL

- Transfusion of platelets
  - Do not expect significant increases if platelets
  - Platelet function in general cannot be improved

- Recombinant VIIIa
  - Will need frequent re-dosing
Renal Disease

- Uremia may cause prolonged bleeding time and abnormal platelet aggregation
  - DDAVP
    - Increases circulating vWF
    - Improves platelet aggregation
  - Cryoprecipitate to increase vWF
Management of Specific Coagulopathies: Acute traumatic coagulopathy
Management of Acute Traumatic Coagulopathy

More to come...
Management of Specific Coagulopathies: The bloody vicious triad
The Bloody Vicious Triad

- Stop the bleeding!
- Focus on the patient’s physiology
- Avoidance of Lethal Triad Conditions
- Early use of blood products → MTP
Stop the Bleeding and Manage Physiology: Damage Control

- Mindset: do as little as needed—arrest the hemorrhage.

- Get the patient to the ICU to help achieve physiologic stability.
Hypothermia

Impact of hypothermia
- Significant decreases seen at <33°C

Effects on coagulation
- Decreased platelet aggregation
- Decreased enzymatic function

Prevention is key
- Fluids
- Rooms
- Use of warmed blankets
Dilution

- Aggravates coagulopathy of Trauma

- Mechanisms
  1. Dilution of clotting factors
  2. Acidosis by hyperchloremia
  3. Hypocalcemia

- Solution
  1. Use of blood products over crystalloids
  2. Massive Transfusion Protocol
Acidosis

- Impact of Acidosis
  1. Significant at pH <7.1
  2. Effect not reversed by pH neutralization

- Mechanism
  1. Inhibition of enzyme complexes

- Prevention and appropriate resuscitation is key
Continued bleeding

- Ongoing nonsurgical bleeding
- May require use of rVIIa
SFGH Guidelines for rVIIa

Guidelines for use of Recombinant Factor VIIa (Novoseven®)

Consider use if the patient has reached Step 3 of the Massive Transfusion Algorithm for Trauma/Neurosurgery Cases (refer to back page of this form for the detailed Algorithm) AND when the following conditions are met:

- Large vessel bleeding controlled with sutures, packs or embolization techniques
- Platelets > 50,000 x 10⁶
- Fibrinogen > 100 mg/dL
- Arterial pH ≥ 7.2

CONTRAINDICATIONS include:

- Do not use until arterial hemorrhage is controlled, either by surgical means, successful packing, or angio-graphic embolization.
- Patients with AIS Grade IV-V intracranial injuries whose coagulopathy is induced by the head injury
- Patients whose injuries are not consistent with long-term survival even if hemorrhage is arrested.
- Patients whose bleeding is uncontrolled and the product is administered as a “last-ditch” effort.

- Initiate Recombinant Factor VIIa (NovoSeven®) at 90 mcg/kg (calculated using ideal body weight) for one single dose.
  
  Note: The in-patient pharmacy will round-down the dose to the nearest vial size.

  Calculated dose of Recombinant Factor VIIa (NovoSeven®):

  90 mcg/kg x ______________________ kg (patient weight) = ______________________ mcg
Coagulopathy is multifactorial

Understanding of causes of coagulopathy aids in selection of appropriate therapy

The understanding of coagulopathies after trauma is in evolution
Thank you!
Fresh Frozen Plasma

Volume: 250-280 ml

Shelf life:
- Frozen – 1 year
- Thawed – hours to days. Use ASAP

Half life:
- V, VIII, (VII) < 12 hours !!

1 unit FFP increase Factors ~3-4% in adults
Platelets

Platelet Units

- Multiple Donors
  - Pooled, typically 6 U in one bag (6-pack)

- Single-Donor
  - Obtained by aphaeresis
  - Equivalent to 6-pack
Platelets

Shelf life: 48 hours

Indications for use:
1. Bleeding and platelet level < 50,000
2. Non-bleeding patient < 10-20,000

<table>
<thead>
<tr>
<th>Expected Increment</th>
<th>1 unit platelets</th>
</tr>
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<tbody>
<tr>
<td>50 lb</td>
<td>22,000/uL</td>
</tr>
<tr>
<td>100 lb</td>
<td>11,000/uL</td>
</tr>
<tr>
<td>150 lb</td>
<td>7,400/uL</td>
</tr>
<tr>
<td>200 lb</td>
<td>5,500/uL</td>
</tr>
</tbody>
</table>