Coagulation Challenges During the Perioperative Period

Linda Liu, M.D.
Professor
Dept Anesthesia and Perioperative Care
UC San Francisco

Waterfall/ Cascade Model: 1960’s

Topics for discussion

• Pre-operative
• Intra-operative
• Post-operative
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Pre-op Bleeding Abnormalities
- Screen by history and physical
  - Congenital
  - Acquired
- Thorough medication list
- Laboratory results - often unable to use an actual number to relate to bleeding risk

Preop: Bleeding History
- Is there a h/o bleeding in family
- Bleeding after procedure
  - Biopsy, tooth extraction, minor surgery
- Experience recurrent nosebleeds
- Experience recurrent gum bleeding
- Experience bruising routinely
- Heavy periods

Congenital factor deficiencies
- Hemophilias, vWD, platelet disorders most common
- Usually present with s/s in early life
- Hematologist involved
- Need treatment before, during, and after surgical procedure
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Acquired coagulation deficiencies
- Medications: heparin, warfarin
- Herbs (gingko, ginseng, garlic)
- Vit K deficiency
- Liver disease
- DIC
- Lupus anticoagulant
- Other acquired inhibitors

Waterfall/ Cascade Model
Extrinsic Pathway (PT)
- Tissue Factor
- fVII
- fII
- Fibrin

Intrinsic Pathway (aPTT)
- Kallikrein
- fXII
- fXI
- fVIII

Coagulation Algorithm
- aPTT prolonged
  - Check for Lupus Anticoagulant (LA)
  - RVV, StaClot, HEXA
- PT prolonged
  - >15.6 sec
  - Repeated
  - FII, FV, FVII FX, fibrinogen levels
  - LA -
  - LA Positive
  - FVIII, FIX FXI levels
- LA -
  - LA Positive
  - Proceed to surgery
  - Hematology consult

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Pre-op to Intra-Op

Intra-op coag abnormalities
• Do not be distracted thinking about zebras if there is intra-op bleeding
  – Surgical
  – Surgical
  – Surgical

Intra-operative bleeding
• Mechanical derangements (surgical)
• Hemodilution
• Hypothermia
• Metabolic derangements (acidosis)
  • Fibrinolysis
  • Consumptive loss (DIC)
Massive blood loss management

- Mainstays
  - Red cells
  - Platelets
  - Fresh frozen plasma
  - Cryoprecipitate
- Active warming
- Frequent labs - electrolytes, acidosis

Massive blood loss management

- Pharmacological interventions
  - Increase clotting
  - Decrease clot breakdown
    - Antifibrinolytics

Coagulation Balance

CLOT LYSIS
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Lysine analogues MOA

Plasminogen → tPA → Fibrin → Lysine analog

Clinical trials

• TxA has been investigated more thoroughly than EACA
• Blood loss is reduced in most studies, but improvement is inconsistent
  – Dosing schedule (3x difference in load)
  – Baseline blood loss in placebo group
• ? efficacy in liver transplantation and orthopedic surgery

Clinical trials

• Multinational, 20,000 patients
• RCT of tranexamic acid in trauma
  – RR 0.91 (95% CI 0.85-0.97) all-cause mortality
  – RR 0.85 (95% CI 0.76-0.96) death due to bleeding
• No evidence of increased clotting, but...

CRASH-2, Lancet, 2010
Clinical Trials Summary

• Decrease RBC transfusion needs
• No current evidence of increased thrombosis risk
• No consensus on effective dosing schedule

Massive blood loss management

• Pharmacological interventions
  – Increase clotting
  – Decrease clot breakdown
  • Antifibrinolytics

Horseshoe Crab

• Genus: Limulus
• Despite name, closer to spiders, ticks, scorpions than crabs
• Almost identical to species living 300 million years ago
• Copper-based blood (hemocyanin)
• Blood detects endotoxin
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Horseshoe Crab Coagulation

- Endotoxin
- Proteases
- Coagulin
- Transglutaminase
- CLOT

Human Coagulation

- Fibrinogen
- Thrombin
- Fibrin
- FXIII
- CLOT

rFVIIa (NovoSeven®)

- Initially developed for hemophilia patients with inhibitors (factor VIII and IX)
- Licensed by FDA 1999
- Deficiencies of other clotting factors
  - V, VII, XI deficiency
- Qualitative or quantitative platelet defects
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Waterfall/ Cascade Model

Intrinsic Pathway

Extrinsic Pathway

Activated Platelet

Common Pathway

Tissue Factor

FVIIa

FVII

fVIII

fX

fII

Fibrinogen → Fibrin

CLOT

Off label use of rFVIIa

• Rescue “life-saving” therapy
  – Trauma
  – Obstetrical
  – Surgical

• Preventative therapy
  – Complex cardiac surgery
  – Liver transplantation

CONTROL trial

• RCT – 150 hospitals, 26 countries
• Trauma patients (blunt and penetrating)
• Enrolled between 4-8 unit of PRBC
• 3 doses of rFVIIa (200 mcg/kg, 100 mcg/kg, 100 mcg/kg)

Hauser et al, J Trauma, 2010
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Stopped Early

• Study was stopped by data monitoring safety board
• High likelihood of futility in demonstrating a difference in primary endpoints - mortality

CONTROL trial

<table>
<thead>
<tr>
<th></th>
<th>rFIIa</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunt</td>
<td>11%</td>
<td>10.7%</td>
<td>0.93</td>
</tr>
<tr>
<td>30 day Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetrating</td>
<td>18.2%</td>
<td>13.2%</td>
<td>0.4</td>
</tr>
<tr>
<td>Transfusions</td>
<td>19 U</td>
<td>23.5U</td>
<td>0.04</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>16.1%</td>
<td>13.2%</td>
<td>0.38</td>
</tr>
</tbody>
</table>

What Happened?

• Expected mortality 30%
• Study mandated use of evidence-based guidelines
  – Transfusion triggers
  – Colloids
  – ARDSnet/ SBT protocols
  – Damage control hemostasis
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Summary of Evidence
• Systematic review and meta-analysis x 3 (including Cochrane)
• 7-13 RCT met inclusion criteria

Ranucci et al, Arch Surg, 143:2008
Stanworth et al, Cochrane, 2008

Mortality rates

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio (95% CI)</th>
<th>Events/Total, No.</th>
<th>Odds Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diprose et al</td>
<td>0.90 (0.91-1.33)</td>
<td>3/10</td>
<td>1/10</td>
</tr>
<tr>
<td>Flavenon et al</td>
<td>1.20 (1.13-1.42)</td>
<td>4/4</td>
<td>1/9</td>
</tr>
<tr>
<td>Sheer et al</td>
<td>3.76 (2.19-7.37)</td>
<td>3/145</td>
<td>0/76</td>
</tr>
<tr>
<td>Lodge et al</td>
<td>1.66 (0.96-3.53)</td>
<td>2/118</td>
<td>0/18</td>
</tr>
<tr>
<td>Lodge et al</td>
<td>0.68 (0.15-3.13)</td>
<td>4/22</td>
<td>2/23</td>
</tr>
<tr>
<td>Friederich et al</td>
<td>Not estimable</td>
<td>0/24</td>
<td>0/12</td>
</tr>
<tr>
<td>Roobottom et al</td>
<td>Not estimable</td>
<td>0/24</td>
<td>0/24</td>
</tr>
<tr>
<td>Total (fixed effects)</td>
<td>0.99 (0.37-2.68)</td>
<td>14/507</td>
<td>6/286</td>
</tr>
</tbody>
</table>

Ranucci et al, Arch Surgery, 2008, 143: 296-304

rFVIIa for ICH
• Use of rFVIIa within 4 hours of intracranial hemorrhage
• Decreased growth in volume of ICH
• Mortality and severe disability was not improved at day 90

Mayer et al, NEJM, 352, 2005
Mayer et al, NEJM, 358, 2008
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FAST trial

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 mcg/kg</th>
<th>80 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>41 (15)</td>
<td>36 (13)</td>
</tr>
<tr>
<td>CVA</td>
<td>8 (3)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Total Arterial</td>
<td>49 (18)</td>
<td>47 (17)</td>
</tr>
<tr>
<td>Total Venous</td>
<td>17 (6)</td>
<td>15 (5)</td>
</tr>
</tbody>
</table>

Diringer et al, Stroke, 41, 2010

Conflicting Information

- Data showing perhaps decrease PRBC transfusion
- No mortality benefit
- More incidence of thrombosis

Expert Recommendations

- Pts not on anticoagulants: most prophylactic uses inappropriate or uncertain
- Ok for rescue in aortic, liver, orthopedic, cardiac surgery, and trauma

Shander et al, Pharm Ther, 2005
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Intra-op to Post-op

Post-op Coagulation Issues
• Bleeding issues resolve or return to operating room
• Imbalance of procoagulants increases risk for thrombotic complications post-op

What’s wrong with heparin?
• Unpredictable anticoagulant response
  – Chemical heterogeneity
  – Extensive protein & cell binding
  – Wide individual variability
• Requires cofactor, anti-thrombin, for efficacy
What’s wrong with heparin?

- **Indirect** thrombin inhibitor
  - Effective on *free* thrombin only
  - Limited inhibition of clot bound thrombin
  - Formed clot not dissolved
- Immunogenic potential: HIT/platelet activation

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**New DTI-Dabigatran etexilate**

- Pradaxa®
- Approved by FDA 10/2010
- In Europe and Canada since 2008
- New oral anticoagulant in > 50 yrs!
- Half life: 12-17 hours
- Esterase metabolism to dabigatran
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Dabigatran Indications
- VTE prevention after hip and knee surgery
- Treat acute DVT/PE and prevention
- Prevent stroke and emboli in nonvalvular AF
- Cardiac events in ACS

Pharmacokinetics
- Low drug-drug or drug-food interactions
- No effect on cytochrome P450 enzymes
- Fixed qD or BID dose
- 80% of drug is eliminated by kidneys

Dabigatran
- No monitoring is recommended except elderly or renal failure pts
- Prolongs PTT, but not linear at high doses
- PT not affected at clinically relevant concentrations
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Reversals
• UFH: protamine
• LMWH: protamine
  – Only partially effective
• Warfarin
  – FFP/ PCC (prothrombin complex concentrates)
  – Vitamin K
  – rFVIIa

POSSIBLE reversals
• Fondaparinux: rFVIIa
• DTIs:
  – DDAVP (in vitro)
  – Cryoprecipitate/ FFP
  – rFVIIA, antifibrinolytic
  – Dialysis

DTI and Regional Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Placement</th>
<th>Wait to restart</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASRA (US)</td>
<td>Suggest avoid</td>
<td>Suggest avoid</td>
</tr>
<tr>
<td>Europeans</td>
<td>8-10 hrs</td>
<td>2-4 hrs</td>
</tr>
</tbody>
</table>

ASRA Practice Advisory, Reg Anesth Pain Med, 2010
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Summary
- Difficult topic to “make easy”
- Impossible to understand without frequent review
- Key points to take home

Summary – pre-op
Intrinsic Pathway (aPTT)
- Kallikrein
  - fXII
  - fXI
  - fIX
- fVIII
- fVII
- Tissue Factor
  - fVII

Extrinsic Pathway (PT)
- Tissue Factor
- fVII

- Def or inhibition fVII, fX, fII, fibrinogen
- Liver disease
- Vitamin K def
- Warfarin effect
- Hemophilia A
- Hemophilia B
- Lupus anticoagulant

Intra-operative bleeding
- Mechanical derangements (surgical)
- Hemodilution
- Hypothermia
- Metabolic derangements (acidosis)
- Fibrinolysis
- Consumptive loss (DIC)
Intra-Op: Clotting

Intrinsic Pathway
- Activated Platelet
- FVIIa
- FVII
- Tissue Factor
- F XIII
- FII
- Fibrinogen
- FVIII
- FII
- Fibrin
- FDP
- EACA
- TxA

Extrinsic Pathway
- Tissue Factor
- FVIIa
- FVII
- FII
- Fibrinogen
- FDP
- EACA
- TxA

Anticoagulants – Post op

- Heparin - HIT
- Warfarin - close monitoring
- Anti-Xa - lack reversal, long acting
- DTI
  - Lack of reversal
  - Lack of experience with regional anesthesia