Coagulation Challenges During the Perioperative Period

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

Waterfall/ Cascade Model: 1960’s

- Intrinsic Pathway
  - Kallikrein
  - fXII
  - fXI
  - fIX
  - fVIII

- Extrinsic Pathway
  - Tissue Factor
  - fX
  - fII
  - fVII
  - Fibrin

Common Pathway
- fX
- fII
- Fibrin

Contact activation (intrinsic) pathway
- Damaged surface
- XII
- XIa
- IX
- VIIIa
- VII

Prothrombin (II)
- Fibrinogen (I)
- Thrombin (IIa)
- Fibrin (Ia)
- XIIIa

Cross-linked fibrin clot
- Active Protein C
- Protein S
- Protein C + thrombomodulin

Tissue factor (extrinsic) pathway
- Trauma
- Antithrombin
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

Topics for discussion
• Pre-operative
• Intra-operative
• Post-operative

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
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

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

Acquired coagulation deficiencies
• Medications: heparin, warfarin
• Herbs (gingko, ginseng, garlic)
• Vit K deficiency
• Liver disease
• DIC
• Lupus anticoagulant
• Other acquired inhibitors

Waterfall/ Cascade Model
Intrinsic Pathway (aPTT)
Kallikrein
fXII
fXI
fIX
fVIII
fVII
fII
Fibrin
• Hemophilia A
• Hemophilia B
• Heparin effect
• Lupus anticoagulant
Extrinsic Pathway (PT)
Tissue Factor
fXII, fX, fII, fibrinogen
• Def or inhibition
• Liver disease
• Vitamin K def
• Warfarin effect

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

Massive blood loss management

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

Coagulation Balance

CLOT  LYSIS

Coagulation Balance

CLOT  LYSIS
Lysine analogues MOA

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 Summary

- Decrease RBC transfusion needs
- Seems effective in trauma patients
- 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

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
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

Waterfall/ Cascade Model

Intrinsic Pathway

Extrinsic Pathway

Activated Platelet

Common Pathway

FVIIa

Tissue Factor

fVIII

fX

fII

Fibrinogen → Fibrin

fVII

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

Stopped Early

- Study was stopped by data monitoring safety board
- High likelihood of futility in demonstrating a difference in primary endpoints - mortality
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

CONTROL trial

<table>
<thead>
<tr>
<th></th>
<th>rFVIIa</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% (actual ~15%)
- Study mandated use of evidence-based guidelines
  - Transfusion triggers
  - Colloids
  - ARDSnet/ SBT protocols
  - Damage control hemostasis

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

Copyright © 2008, American Medical Association. All rights reserved.
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

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

FAST trial

<table>
<thead>
<tr>
<th></th>
<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>
<td>64 (22)</td>
</tr>
<tr>
<td>CVA</td>
<td>8 (3)</td>
<td>11 (4)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Total Arterial</td>
<td>49 (18)</td>
<td>47 (17)</td>
<td>82 (28)</td>
</tr>
<tr>
<td>Total Venous</td>
<td>17 (6)</td>
<td>15 (5)</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 from drug alone, more from other evidence based transfusion practices
- 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
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
- Requires cofactor, anti-thrombin, for efficacy
  - Effective on free thrombin only
  - Formed clot is not dissolved
- Immunogenic potential: HIT/platelet activation

Coagulation Cascade

[Diagram showing the coagulation cascade with intrinsic and extrinsic pathways, including fVIII, fX, fII, fVII, Antithrombin, Heparin, Tissue Factor, and DTI.]
New DTI-Dabigatran etexilate

- Pradaxa®
- Approved by FDA 10/2010
- New oral anticoagulant in > 50 yrs!
- In Europe and Canada since 2008
- Half life: 12-17 hours
- Esterase metabolism to dabigatran

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
Coagulation Cascade

Intrinsic Pathway
- Activated Platelet
- fVIII
- vWF
- Antithrombin
- Heparin

Extrinsic Pathway
- Tissue Factor
- fXII
- fXIII
- DTI
- Fibrin

Fondaparinux (Arixtra®)
- Synthetic LMWH
- Five saccharide units
- Binds and activates antithrombin
- Effective in inhibiting fXa
- Measure with anti-Xa activity assay

Fondaparinux
- Half-life: 21 hours
- Given SC daily
- Cousin: idraparinux
  - Half life: 80 hours
  - Q week dosing!
- Neither require routine monitoring

Who Cares?
- We usually don’t prescribe
- Pts will come for emergent surgery
  - How do we reverse it?
- How does this affect regional anesthesia?
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

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

Anticoagulants + regional anes
- Guidelines not based on randomized controlled trials
- Instead: case reports, retrospective reviews, limited small studies, or theoretical knowledge of pharmacokinetics and pharmacodynamics

Lepirudin and Regional Anes

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

ASRA Practice Advisory, Reg Anesth Pain Med, 2010
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

Dabigatran Package Insert
- If possible, discontinue PRADAXA 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures risk
- Consider longer times for patients undergoing spinal puncture, or placement of a spinal or epidural catheter

Fondaparinux and Regional Anes

<table>
<thead>
<tr>
<th>Placement</th>
<th>Wait to restart</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASRA (US)</td>
<td>Single, atraumatic pass No indwelling catheters</td>
</tr>
<tr>
<td>Europeans</td>
<td>36-42 hrs</td>
</tr>
</tbody>
</table>

ASRA Practice Advisory, Reg Anesth Pain Med, 2010

Recommendations-General
- Monitoring should be at least q2-4 hours x 12 hours
- Infusion should be limited to drugs that minimize sensory and motor block

Summary
- Difficult topic to “make easy”
- Impossible to understand without frequent review
- Key points to take home
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

Summary – pre-op

**Intrinsic Pathway (aPTT)**

- Kallikrein
  - fXII
  - fXI
  - fIX
  - fVIII

**Extrinsic Pathway (PT)**

- Tissue Factor

- Def or inhibition
- fVII, fX, fII, fibrinogen
- Liver disease
- Vitamin K def
- Warfarin effect

- Hemophilia A
- Hemophilia B
- Heparin effect
- Lupus anticoagulant

Intra-Op: Clotting

**Intrinsic Pathway**

- Activated Platelet
  - FVIIa

**Extrinsic Pathway**

- Tissue Factor
  - fVII
  - fX
  - fII

- Fibrinogen → Fibrin

- EACA
- TxA
- FDP

Anticoagulants – Post op

- New anticoagulants (fX, thrombin)
  - Increased use in community
  - Lack reversal
  - Long acting
  - Lack of experience with regional anesthesia

Coagulation, Blah, Blah, Blah, Blah, Blah, Blah, Blah, Blah, Blah, Blah, Blah,……zzzZ
Postoperative Pain Management in the Older Patient
Linda Liu, M.D.

Coagulation Cascade

Questions?