New Hemostatic Strategies in Trauma and Surgery: Focus on Antifibrinolytics and Factor Products

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Learning Objectives

• Compare the members of the antifibrinolytic class and describe their use in surgical hemostasis
• Describe the role of tranexamic acid (TXA) in traumatic hemorrhage based on the findings of the CRASH-2 trial
• Explain current recommendations for indications and dosing strategies for the various factor products used in traumatic hemorrhage

The presenters have no actual or potential conflicts of interest to disclose.

Core Concepts: Blood Conservation1-3

Core Concepts: DCR4,5

Core Concepts

Antifibrinolytics: Overview6-9

• Mechanism
  • Interfere with chemical mediators of fibrinolysis → ↑ hemostasis
• Original indications
  • Limit blood loss in CABG
  • Reduce bleeding in hemophilia
• Inpatient uses (off-label)
  • Reduce transfusion requirement in surgery
  • Reduce mortality in traumatic hemorrhage
### Antifibrinolytics: Aprotinin⁹-¹¹

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Low-Dose</th>
<th>Full-Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000,000 KIU LD</td>
<td>2,000,000 KIU</td>
<td>1,000,000 KIU CPB</td>
</tr>
<tr>
<td>250,000 KIU/hr IV</td>
<td>500,000 KIU/hr</td>
<td>1,000,000 KIU CPB</td>
</tr>
</tbody>
</table>

Mechanism
- ↓ plasmin
- ↓ kallikrein, thrombin, GP binding

Effects
- antifibrinolytic
- anti-inflammatory
- antithrombotic
- platelet protection

> maintain physiologic hemostatic balance

KIU = kallikrein inactivator units; 100,000 KIU = 14 mg aprotinin

### Antifibrinolytics: Lysine Analogues⁶-¹⁰

#### Members:
- ε-aminocaproic acid (ACA, Amicar®)
- Tranexamic acid (TXA, Cyklokapron®)

#### Mechanism:
- Bind to lysine receptors on plasminogen → prevent activation to plasmin → prevent plasmin-mediated degradation of fibrin = ↓ fibrinolysis

#### Antifibrinolytics: Lysine Analogues⁷⁻¹¹,¹²⁻¹⁶

<table>
<thead>
<tr>
<th>Cardiac Surgery</th>
<th>ACA</th>
<th>TXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10g or 75-100mg/kg LD</td>
<td>1-2g or 10-30mg/kg</td>
<td>0.4-1g/hr or 1-16 mg/kg/hr</td>
</tr>
<tr>
<td>1 g/hr or 10-15 mg/kg/hr IV*</td>
<td>0.5-2g or 2mg/kg to</td>
<td>0.5-2g or 2mg/kg to</td>
</tr>
<tr>
<td>2-2.5 g/L of CPB</td>
<td>↓ rate in renal insuff.</td>
<td></td>
</tr>
<tr>
<td>10g + 10g + 10g</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ortho Surgery**
- 5-10g or 100mg/kg LD
- 1-3 g/hr IV

- 1g or 10-15mg/kg
- 1-10 mg/kg/hr
- 10-15 mg/kg bolus x2
- 10-20 mg/kg bolus x1

### Antifibrinolytics: Aprotinin

- Withdrawn from market after 2008 BART study (RCT, n=2331)¹¹
- 30-day mortality: aprotinin > TXA (p=0.05), aprotinin > aminocaproic acid (p=0.06)
- Subsequent meta-analyses¹,⁷,¹²
  - Somewhat inconclusive, generally confirm
  - Mortality, aprotinin vs. lysine analogues¹: RR=1.49 (95%CI 1.12-1.98), I²=0%, n=5154
  - Reintroduced in international markets
  - Restricted to investigational use in U.S.

### Antifibrinolytics: Lysine Analogues⁶⁻¹⁰

#### PK:
- TXA ~10x more potent than ACA but ≠ clinical superiority
- Short t½, renal elimination

#### Dosing:
- Varies by procedure type
- Weight- and non-weight-based regimens studied
- Superior regimen yet to be identified

### Antifibrinolytics: Lysine Analogues⁶,⁹,¹⁷⁻²⁰

#### Adverse reactions:
- Rate-related hypotension/bradycardia
- Post-op AKI (ACA>TXA)
- Post-op seizures (TXA>ACA)
- VTE?
Antifibrinolytics: Cardiac Surgery

- Lysine analogues recommended as blood conservation strategy\(^1\)
- 2011 Cochrane review for ↓transfusion\(^7\)
  - TXA vs. ACA:
    - RR=0.97 (95%CI 0.77-1.21), I\(^2\)=50%, n=2003
- 2011 analysis of 2008 BART trial data\(^21\)
  → ACA agent of choice
  - Comparable safety/efficacy → consider cost (~$250 vs. ~$2.50 per case)

Antifibrinolytics: Ortho Surgery

- 2006 meta-analysis of antifibrinolytics in orthopedic surgery\(^13\)
  - Included aprotinin, ACA, TXA
  - ↓transfusion, TXA vs. placebo:
    - OR=0.17 (95%CI 0.11-0.24), n=796
  - ↓transfusion, ACA vs. placebo:
    - OR=0.71 (95%CI 0.29-1.73), n=92

Antifibrinolytics: Ortho Surgery

- 2011 analysis of 2008 BART trial data\(^21\)
  → ACA agent of choice
- Comparable safety/efficacy → consider cost (~$250 vs. ~$2.50 per case)

Antifibrinolytics: Topical TXA\(^22-24\)

- Theory: reduce bleeding without exposure to AEs (VTE, seizures, AKI)
- Studied regimens:
  - Cardiac: TXA 1-2.5 g in 100-250 mL as irrigation prior to sternotomy closure
  - Ortho: TXA 0.25-3 g in 20-100 mL irr
- (+): Significantly ↓ blood loss in RCTs
- (-): Inconsistent ↓ in transfusion, minimal safety data

Antifibrinolytics: Surgery Use at GMC

- Cardiac surgery:
  → ACA 10g/40mL slow IVP at induction, intra-operatively, and at end of CPB
- Orthopedic surgery:
  → TXA 20mg/kg (max 2000mg) IVPB in NS 100mL x1 given over 30-60mins at induction + LMWH post-op for DVT ppx
- Drug shortages...
Antifibrinolytics: Trauma

• CRASH-2 trial\textsuperscript{25} provides Level 1 evidence for TXA ↓ mortality
  • Large, international, double-blind RCT
  • Civilian trauma + significant bleeding
  • N=20,211 randomized within 8 hr
    • TXA 1 g over 10 mins + 1 g over 8 hr or matching normal saline placebo
  • Primary outcome: in-hospital death from any cause within 28 days

Antifibrinolytics: Trauma

• 2010 CRASH-2 trial\textsuperscript{25}
  • No apparent demographic differences
  • TXA associated with ↓ 28-day mortality
    • 14.5\% vs. 16.0\%, RR=0.91 (95\% CI 0.85-0.97), n=20,127 \n  • Also with ↑ survivors w/o dependency
  • No significant differences in vascular occlusive events (exc. ↑MI in placebo)
  • No significant differences in transfusion or surgery requirements

Antifibrinolytics: Trauma

• Additional CRASH-2 analyses:
  • Importance of early treatment\textsuperscript{26}
  • Greatest benefit in most severe, but all with >5\% risk of death benefited\textsuperscript{27}
  • No apparent improvements or harms in TBI subgroup analysis\textsuperscript{28}
  • Findings confirmed by Cochrane meta-analysis\textsuperscript{29}, RCT in military trauma\textsuperscript{30}

Antifibrinolytics: Trauma

• Limitations and unanswered questions:
  • Optimal dosing regimen?
  • Use in anti-coagulated patients?
  • Use in ICH?
  • Combination with factor products?
  • Use in pre-hospital setting? Other conditions?

Antifibrinolytics:

Trauma Use at GMC

• Eligible trauma patients:
  • Require inpatient blood transfusion or MTP
  • Excluded: anti-coagulated patients, cardiopulmonary arrest
  • Bolus compounded by RPh
    • 1g/100mL NS over 10 min
  • Infusion prepared in central pharmacy
    • 1g/500mL NS over 8 hrs

Antifibrinolytics: Summary Points

• ACA may be the preferred anti-fibrinolytic for limiting peri-operative blood loss in cardiac surgery due to comparable safety and efficacy but lower cost compared to TXA
• TXA may be preferred in non-cardiac surgery indications due to a higher volume of evidence and extremely limited comparative efficacy data with ACA in these settings
Antifibrinolytics: Summary Points

• A superior dosing regimen for either antifibrinolytic in any surgery indication has yet to be established
• TXA should be used in a standardized protocol to mitigate mortality in trauma patients with life-threatening hemorrhage based on the results of the CRASH-2 trial

rFVIIa (Novoseven®)\(^{31-32}\)

• Approved uses:
  • Treatment and prevention of bleeding in patients with hemophilia with coagulation factor inhibitors: 90mcg/kg q2hr until hemostasis achieved (35-120mcg/kg)
  • Acquired hemophilia: 70-90mcg/kg q2-3hr until hemostasis achieved
  • Congenital factor VII deficiency: 15-30mcg/kg q4-6hr until hemostasis achieved
• Off-label uses: surgical prophylaxis, uncontrolled bleeding (i.e. trauma, cardiac surgery, liver disease)
• Cost: 1000mcg vial = $1720 (AWP)

Use of Activated Recombinant Factor VII (rFVIIa) and Prothrombin Complex Concentrate (PCC) in Surgery and Trauma

Mechanism of Action

Coagulopathy of Trauma\(^{32}\)

CONTROL Trial\(^{33}\)

• Phase III randomized trial comparing rFVIIa vs. placebo in blunt and/or penetrating trauma
• rFVIIa group received 200mcg/kg initially then 100mcg/kg at 1 hour and 3 hours
• Primary outcome: 30-day mortality
• Secondary outcomes: organ failure at 30 days, volume of blood products transfused at 24 and 48 hours, incidence of major complications
• Trial was terminated early due to being underpowered for its primary endpoints
• Significant reduction in massive RBC transfusion from injury to 24 hours post-dose (p=0.04)
• Thrombotic complications were similar between groups
Warfarin-Induced Intracranial Hemorrhage (ICH)\(^3\) 
- Retrospective chart review on 24 patients with warfarin-induced ICH that received rFVIIa 
- Dosing: 
  - \(<\) 100kg = 1200mcg 
  - \(\geq\) 100kg = 2400mcg 
- Increased survival rate (93%) in patients that received FFP, IV vitamin K and rFVIIa compared to patients that received one or two treatment modalities (33%) 
- No adverse events were recorded

AHRQ Summary

**Adult cardiac surgery**
- No significant effect on mortality, RBC transfusion rates or ICU length of stay 
- Significant increased risk for thromboembolic rates vs usual care

**Body trauma**
- No consistent effects on mortality. Possible reduction in acute respiratory distress syndrome 
- No effect on thromboembolic events

**Spontaneous intracranial hemorrhage**
- No effect on mortality or functional outcomes. Less hematoma progression. 
- Increased risk for arterial thromboembolic events in doses \(>\) 40mcg/kg

Comparative Effectiveness of rFVIIa for Off-Label Uses vs Usual Care in the Hospital Setting (2010)\(^4\)
- Agency for Healthcare Research and Quality (AHRQ) wanted to determine the usage patterns of rFVIIa and effectiveness in trauma, ICH, cardiac surgery, liver transplantation, and prostatectomy 
- Examined data from a database of 615 U.S. hospitals from 2000–2008 as well as performed an extensive literature review

Cochrane Database Meta-Analysis of rFVIIa Use in Patients without Hemophilia\(^5\)
- Originally published in 2007, updated in March 2012 
- Included 29 randomized control trials 
  - 16 trials examined prophylactic use 
  - 13 trials examined therapeutic use 
- No difference between low dose (\(<\) 80mcg/kg) and high dose (\(\geq\) 80mcg/kg) 
- No evidence of dose-response effect or mortality benefit 
- Decreased blood loss and transfusion requirements 
- Trend toward ↑ in arterial thromboembolic events 
- Use of rFVIIa should be limited to clinical trials and ONLY used for its current licensed indications

Reversal of Bleeding Associated with Direct Thrombin Inhibitors (DTI) or Factor Xa Inhibitors (FXa)\(^6\)
- Few small-scale animal studies and human case reports 
- One case report did not show a decrease in the progression of ICH in a patient taking dabigatran 150mg bid after a ground-level fall

OhioHealth rFVIIa Prescribing Guidelines
- Intracranial hemorrhage on warfarin 
  - Receive FFP and 10mg IVPB of vitamin K 
  - \(<\) 80kg – 1000mcg x 1 
  - \(\geq\) 80kg – 2000mcg x 1 
  - Repeat INR 1-2hr after infusion & may re-dose if INR > 1.4 
- Blunt or penetrating trauma 
  - 100mcg/kg (ABW) x 1 
  - May repeat in 1hr
Prothrombin Complex Concentrate (PCC)\textsuperscript{37-38}

- In Europe, PCC has been used for anticoagulation associated hemorrhage or for reversal for anticoagulation for emergent surgery
- Smaller volume to be administered than FFP and has faster onset than vitamin K
- 2012 ACCP guidelines recommend PCC (4-factor) over FFP to manage major bleeding
- Cost: 1 vial = $480 (AWP)

FEIBA for Warfarin Reversal in Life-Threatening Bleeding\textsuperscript{41}

- Retrospective chart review of 72 patients who received FEIBA and 69 patients who received FFP
- FEIBA cohort received 500 units if INR < 5 and 1000 units if INR ≥ 5 + vitamin K 10mg IVB
- Primary endpoint was INR normalization and secondary endpoint was survival
- >50% achieved an INR ≤ 1.4 versus 33% of the patients that received FFP
- Time that elapsed from administration of treatment to INR ≤ 1.4 was shorter for FEIBA
- No difference between groups in survival or length of hospital stay
- 5 patients in FEIBA group experienced adverse events (1 upper extremity DVT around a PICC)

Beriplex for Emergent Anticoagulation Reversal\textsuperscript{40}

- Single-arm prospective multi-national study
- 43 patients were included in the study
- PCC dose:
  - 25 IU/kg for INR 2 – 3.9
  - 35 IU/kg for INR 4 – 6
  - 50 IU/kg for INR > 6
- 38 patients (88%) received IV/PO/SC vitamin K (dose range: 5-20mg)
- INR declined to ≤ 1.3 in 40 patients (93%)
- Clinical hemostatic efficacy achieved in 40 patients (93%)

PCC vs. rFVIIa in Reversing Coagulopathy of TBI\textsuperscript{42}

- Retrospective chart review at level 1 trauma center of all patients with TBI and induced or acquired coagulopathy who received PCC or rFVIIa during a 4 yr period
- 85 TBI patients were included
  - 64 patients received PCC 25 IU/kg
  - 21 patients received rFVIIa 90 mcg/kg
  - 31 patients on warfarin (44% of PCC vs. 14% of rFVIIa)
- Significant decline in RBC transfusions and FFP after PCC administration
- No significant difference in craniotomy rates
- Statistically significant lower mortality rate in PCC group versus rFVIIa (67% vs 47%, p=0.02)
- 1 thromboembolic event in a rFVIIa patient
- Mean cost was $1,007 for PCC vs. $5,757 for rFVIIa

Reversal of Bleeding Associated with DTI or FXa

- Study conducted in healthy volunteers that received dabigatran showed no decrease in the anticoagulant effect when they received 4 factor PCC (50 units/kg) but DID decrease the effect of rivaroxaban\textsuperscript{43}
- Isolated case reports of low dose FEIBA being effective in reversing dabigatran\textsuperscript{37}
- Ex vivo studies demonstrate FEIBA MAY be a potential reversal agent for FXa\textsuperscript{37}
OhioHealth PCC Prescribing Guidelines

- Traumatic or spontaneous head injury on warfarin anticoagulation with confirmed ICH on CT scan
- Should receive FFP and 10mg IVPB vitamin K
- INR 1.4 – 2.9 = 25 units/kg
- INR 3 – 5.9 = 35 units/kg
- INR ≥ 6 = 50 units/kg
- May re-dose in 1 hour if INR remains ≥ 1.4
- For rivaroxaban = 50 units/kg

Summary Points

- Optimal dosing and timing of rFVIIa has not been determined in non-hemophiliacs
- rFVIIa may be more beneficial in the course of resuscitation rather than as a last-ditch effort
- More literature support for the use of PCC to treat both acquired and induced coagulopathy in TBI with or without warfarin use
- PCC may be an effective reversal agent for the newer oral anticoagulants

Questions and Discussion

Hemostasis
- Antifibrinolytics
- Factor Products

Hemorrhage
- Surgical Blood Loss
- Traumatic Coagulopathy

DCR Blood Conservation

Surgical Blood Loss Traumatic Coagulopathy
New Hemostatic Strategies in Trauma and Surgery: Focus on Antifibrinolytics and Factor Products
Dave Robinson, PharmD and Sara Jordan, PharmD – 5/2/13 OSHP

References:


34. Dickson AL, Burns LL. Retrospective evaluation of recombinant factor VIIa (rVIIa) in warfarin-induced intracranial hemorrhage. Presented at the ASHP Midyear Meeting, 2005.