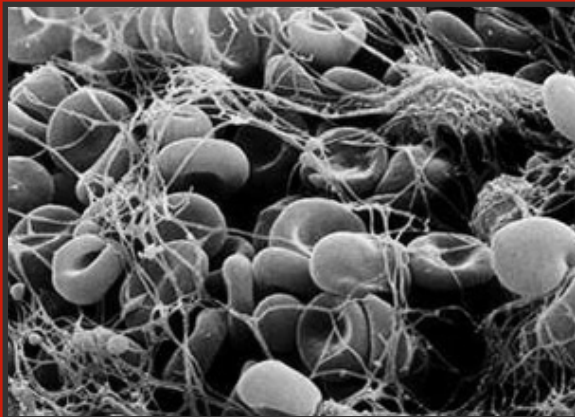


Approach to a Bleeding Patient

Frontiers in Transfusion Medicine
November 14, 2009

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Conflict of Interest

- Nothing to disclose

Case

- It is a lovely Thanksgiving weekend
- Mr. Smith, a 69 year old retired engineer, decides to clean the eaves troughs
- The ladder wobbles and Mr. Smith falls hitting his head on the concrete driveway
- His cries for help are heard by the neighbour who promptly calls 911...



Case

- In the ER...
 - Mr. Smith is awake and responds appropriately
 - Vitals are stable
 - On exam, bruising/superficial bleeding is noted

Case

- Laboratory Tests
 - Hb 125, platelets 155
 - INR 3.43, PTT 37



Case

The next step should be (pick the best answer):

- (A) Order more lab tests
- (B) Give 5 mg vitamin K sc
- (C) Infuse 1,000 units of Octaplex
- (D) Infuse 1.2 mg rVIIa
- (E) Transfuse 4 units FP

Case

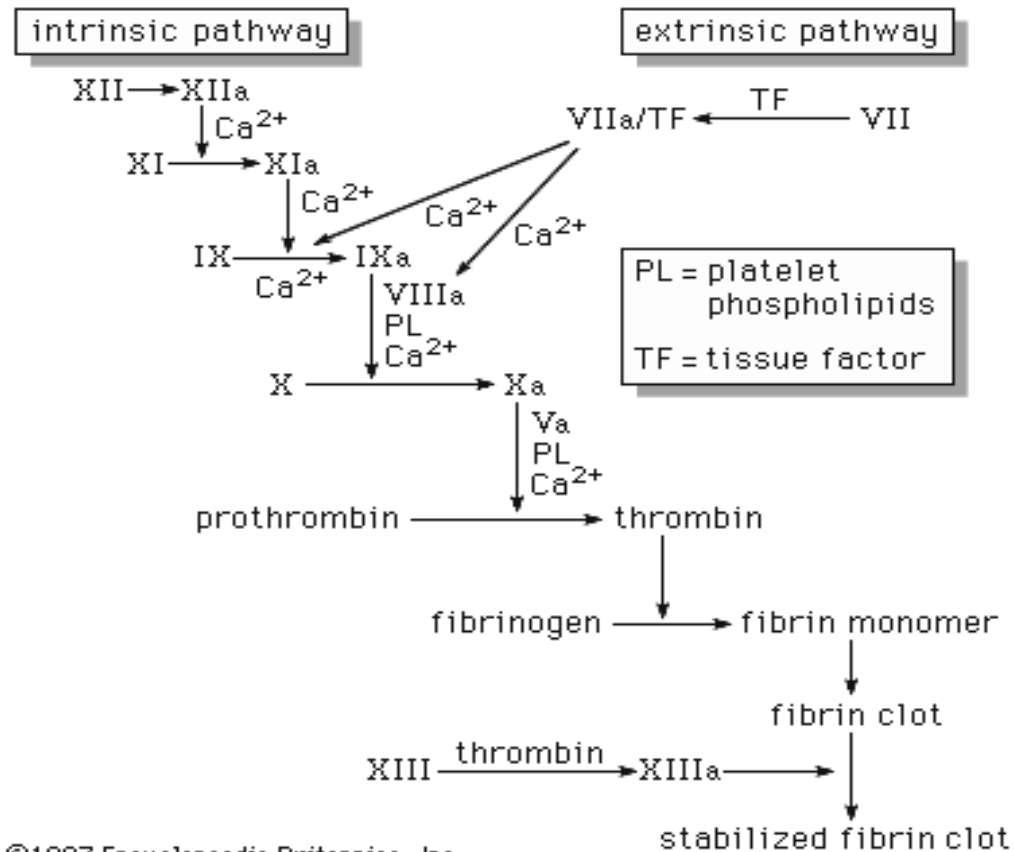
- We decided to do more laboratory tests...
 - Factor II 0.26
 - Factor V 1.22
 - Factor VII 0.09
 - Factor IX 0.38

Case

Pick the best answer:

- (A) Tests consistent with Vitamin K deficiency
- (B) Tests consistent with early coagulopathy of trauma
- (C) Tests consistent with liver disease
- (D) Tests consistent with DIC
- (E) I do not know what this means

Coagulation Cascade



Significance of PT/INR

- Measure of extrinsic and final common pathway
 - function of FVII, X, V, II and fibrinogen
- Common causes of elevated INR
 - Vitamin K deficiency
 - Liver disease
 - Specific factor deficiency – FII, FVII, or FX

What to do?

- Do not wait for a bleeding emergency. Figure out what the cause.
- Call an expert: hematologist or hematopathologist
- 50:50 mix (1:1 mix)
 - Patient plasma is mixed with normal plasma
 - Correction – c/w deficiency
 - No correction – inhibitor
- Factor levels

What not to do?

“in vivo 50:50”



Vitamin K Deficiency

- Vitamin K
 - Required for synthesis of protein C and S as well as coagulation factors II, VII, IX and X
 - Fat soluble vitamin derived from food and produced by gut flora
 - Body stores are low

Vitamin K Deficiency



1 factor X

9 factor IX

7 factor VII

2 factor II

Canada protein C

Soviet Union protein S

Vitamin K Deficiency

- Etiology
 - Anticoagulation with warfarin, lack of oral intake, antibiotics, malabsorption
- Laboratory Investigations
 - INR elevated, PTT normal
 - Vitamin K dependent factors low
- Clinical
 - Bruising, bleeding after trauma or invasive procedures, intracranial hemorrhage

Back to Case

- Is Mr. Smith at risk for vitamin K deficiency?
- We obtain more history...
 - Distraught Mrs. Smith arrives in the ER and reports that Mr. Smith has been well and he takes a blood pressure pill and another pill to prevent blood clots.



Case

- In the meantime, Mr. Smith is getting somnolent and the nurse has difficulty waking him up
- A head CT scan is ordered...

Mr. Smith – CT head



Case

- Mr. Smith has an acute traumatic subdural hematoma
- The staff neurosurgeon reviews the scan and recommends urgent operative intervention

Warfarin in Traumatic Brain Injury

- 6 studies have demonstrated a positive direct correlation between warfarin consumption before TBI and mortality rate (MR) when compared with control groups
 - Absolute difference in MR was 19-30% regardless of injury severity
 - Increasing age was an independent predictor of mortality
 - MR increased with increasing pre-injury INR

Case

The next step should be:

- (A) Give 10 mg vitamin K IV
- (B) Transfuse 4 units FP
- (C) Infuse 1,000 units of Octaplex
- (D) Infuse 1.2 mg rVIIa
- (E) Both A and C

Vitamin K

- Most patients will have substantial reduction in INR within 6-12 hours of receiving IV vitamin K
- Oral vitamin K may take 12-24 hours
- Do NOT administer Vitamin K IM (increases risk of hematoma) or SC (less effective than oral or IV forms)



How to manage elevated INR due to warfarin

| Condition | Recommendation |
|---|--|
| INR <5, stable | Hold warfarin and adjust dose |
| INR 5-9, stable | Hold warfarin and give vitamin K 1-2.5 mg po |
| INR >9, stable | Hold warfarin and give vitamin K 5-10 mg po |
| INR > 1.5 and major bleeding OR urgent major surgical procedure | Hold warfarin Give vitamin K 10 mg IV FP 3-4 units OR Octaplex 1,000 U |

Adapted from Ansell J *et al*, Chest 2004;126:204S-33S

PCC (Octaplex)

- Derived from pooled human plasma and pathogen inactivated
- Contains FII, VII, IX, and X and proteins C and S
- Supplied as lyophilized powder in vials of 500 IU FIX



PCC (Octaplex)

- Indication
 - **Emergency reversal** of warfarin therapy (life-threatening bleeding or emergency surgery) **AND INR>1.5**

PCC (Octaplex)

- Dose
 - NAC guidelines
 - 1,000 IU (40 cc, 2 vials) for patients weighing 50-90 kg and INR 1.5-4.0
 - For weights or INRs outside of these ranges, consult transfusion medicine or hematology
 - Package insert

Table 1: Approximate Doses of OCTAPLEX Required for Normalization of INR

| Initial INR | 2-2.5 | 2.5-3 | 3-3.5 | >3.5 |
|--|---------|---------|---------|------|
| Approximate dose* (mL OCTAPLEX/kg body weight) | 0.9-1.3 | 1.3-1.6 | 1.6-1.9 | >1.9 |

* The single dose should not exceed 3,000 IU (120 mL Octaplex).

PCC (Octaplex)

- Administration
 - Following reconstitution, inject by **slow** IV push (initial rate 1 cc/min for 5 minutes then 2-3 cc/min until done) OR
 - Transfer reconstituted product into a small IV bag and infuse slowly
- Monitoring
 - Check INR immediately post infusion and 4-6 hours post infusion

FP vs. PCC

- FP

- Human
- No viral inactivation
- Large volume (15 mL/kg; 770-1500 mL)
- Risk of TRALI, TACO and anaphylaxis
- Needs to be thawed
- Requires ABO group

- PCC

- Human
- Virally inactivated, prion reduction process
- Small volume 40-80 mL
- Risk of thrombosis, allergic reaction
- Lyophilized, needs to be reconstituted
- Does not require ABO group
- Contraindicated in HIT (trace heparin)

What about rVIIa?

- 8 studies address warfarin related CNS bleeding
 - All show that rVIIa rapidly corrects INR
 - Clinical impact is not clear
 - Retrospective, case reports or case series, number of patients per study 1-16, no adequate controls
 - Co-administration of other hemostatic therapy (FP, etc.)
 - Recommendation: against routine use of rVIIa in acute warfarin reversal

Conclusions so far...

- Do not climb ladders especially if taking warfarin...
- Always investigate a new coagulopathy to allow appropriate management
- Be aware of the risks and benefits of alternative therapies

Approach to a Bleeding Patient

- 1. ABC
- 2. Pertinent **history** of bleeding
 - Provoked versus spontaneous
 - Immediate versus delayed (>20 minutes)
 - Known bleeding disorder
 - Conditions associated with bleeding (liver failure, kidney failure, etc.)
 - Medications causing bleeding (warfarin, clopidogrel, etc.)
 - Interventions so far (and their effect)

Approach to a Bleeding Patient

- Physical examination
 - Where (localized versus diffuse), how much and how long
 - Useful hints:
 - Petechiae, mucosal bleeding – low/dysfunctional platelets
 - Bleeding into muscles/joints – hemophilia
 - Flank hematoma – retroperitoneal bleeding

Approach to a Bleeding Patient



Approach to a Bleeding Patient

- Laboratory Investigations
 - Point of care testing if available
 - Hg monitoring, TEG (thromboelastography)
 - Poorly studied but results are immediately available
 - CBC – hemoglobin, platelet count
 - PT/INR, PTT, fibrinogen, thrombin time
 - if abnormal, replace and/or investigate further

Approach to a Bleeding Patient

- Management (as per ATLS, ASA, etc.)
 - Assess need for surgical hemostasis
 - Maintain $\text{plt} > 50$ in any bleeding patient, > 100 in head trauma/neurosurgical patient
 - Maintain $\text{Hb} > 80$ g/L
 - Maintain $\text{PT} < 1.5x$ and $\text{PTT} < 1.5x$ normal
 - Maintain fibrinogen > 1 g/L
 - Correct acidosis, hypothermia, hypocalcemia

Approach to a Bleeding Patient

- Problems with laboratory-based resuscitation
 - Not based on good evidence
 - Rely on fast TAT for coagulation testing
 - Based on assumption that coagulation tests accurately predict *in vivo* hemostatic capacity
 - Based on the assumption that coagulopathy develops late

Approach to a Bleeding Patient

- Problems with ratio-based resuscitation (1:1)
 - Based on poor evidence (retrospective studies, no adequate controls, survivorship bias)
 - Unable to accurately predict who will require a massive transfusion
 - Higher risk of transfusion related complications (acute lung injury, circulatory overload, etc.)

General Approach

- What to do?
 - A pilot RCT is taking place at Sunnybrook
 - Once >6-10 units of PRBC have been transfused, consider ratio-based resuscitation (1:1 plasma to PRBC)

Bottom line...



...Clinical equipoise

Approach to a Bleeding Patient

- Management
 - Consider specific treatment for coagulopathy
 - If known bleeding disorder and specific treatment available
 - Reverse anticoagulation if applicable (protamine)
 - Consider antifibrinolytics

Approach to a Bleeding Patient

- What about rVIIa?
 - 2009 Cochrane review
 - “Clinical value of rFVIIa as a more general hemostatic drug, both as prophylaxis prior to high blood loss surgery or as therapy to treat uncontrollable bleeding remains unproven”

Outline of Presentation

- Approach to abnormal INR/PT
- Approach to warfarin reversal in a bleeding patient
- Approach to a bleeding patient
 - Lab-based resuscitation versus 1:1 plasma to PRBC resuscitation
 - rVIIa use in a bleeding non-hemophilia patient