Disclosures:
- I have no conflicts of interest to disclose

Objectives
- Review some of the challenges of coagulopathy & trauma
- Discuss new treatments for trauma induced coagulopathy, including:
  - Tranexamic Acid (TXA)
  - Prothrombin Complex Concentrate (PCC)
  - Recombinant Factor VIIa
  - Fibrinogen Concentrate
- Discuss the use of Trauma Anesthesia checklists

TRAUMA Epidemiology
- Major cause of Mortality worldwide, 5 million deaths annually.
- Disease of the young, leading cause of "Years of life lost"

Coagulopathy & Trauma
- Exsanguination due to uncontrolled bleeding is the leading cause of potentially preventable deaths among trauma patients
- 1/3 of trauma patients are coagulopathic on admission
- Coagulopathy is associate with significantly higher mortality
  - In patients with the same Injury Severity Score, the presence of coagulopathy nearly doubled mortality
- Correction of coagulopathy is one of the primary goals of trauma anesthesia
Pathophysiology of Trauma-induced Coagulopathy

- Loss Coagulopathy
- Dilutional Coagulopathy
- Consumption Coagulopathy
- Hyperfibrinolysis
- Hypothermia
- Acidosis
- Anemia
- Electrolyte disturbances

Risk factors for Hyperfibrinolysis in Trauma:

- Liver failure
- Increased Injury Severity Score
- Hypotension
- Hypothermia
- #RBCs transfused
- Worsening Base Deficit
- Lactate levels
- Higher Crystalloid use

Emerging treatments for Trauma induced Coagulopathy

- Point of Care driven transfusion strategy (TEG or ROTEM)

Incidence of Hyperfibrinolysis

- Varies widely in trauma
  - 2-15% of trauma patients on arrival
  - 34% of trauma patients requiring massive transfusion (>10 units) (DH)
- Most studies use TEG for diagnosis
- Defined as LY30 > 7.5% or EPL > 15% on r-TEG

Hyperfibrinolysis

- Fibrinolysis is an important component of normal balance between clot formation and breakdown
- When this becomes pathologic = hyperfibrinolysis
- Etiology is likely related to alterations in Protein C anticoagulation pathway
- Results in non-surgical bleeding

Hyperfibrinolysis in Trauma

- Hyperfibrinolysis independently and significantly predicts mortality in trauma patients
- Mortality rate of 73–100% depending on degree detected
- Even low levels of hyperfibrinolysis predicts poor outcome in trauma
- LY30 > 3% is associated with initial significant increase in mortality
Hyperfibrinolysis on TEG

- TEG provides real-time diagnosis of hyperfibrinolysis
- Use of rTEG may reduce this extremely high mortality of trauma patients with fulminant hyperfibrinolysis

Antifibrinolytics

- Antifibrinolytics have been thoroughly investigated in multiple surgical settings including cardiac, orthopedic, liver transplant and trauma (extensively)

Tranexamic Acid (TXA)

- Synthetic derivative of Lysine, irreversibly inhibits the proteolytic action of plasmin on fibrin clot and platelet receptors
- Inhibits fibrinolysis
- Reduces transfusion requirement by 30% in elective surgery

TXA–CRASH-2

- Largest randomized placebo-controlled trial reporting effect of early TXA
  - Significant reduction in all-cause mortality with TXA
    - 14.5% vs 16% (p=0.035)
  - Significant reduction in risk of death due to bleeding with TXA
    - 4.9% vs 5.7% (p=0.0077)
  - No increase in fatal or non-fatal vascular occlusive effects
  - Early treatment (<1hr from injury) had the greatest reduction in mortality

- Subsequent analyses of CRASH-2
  - Benefit of TXA was only seen when given within 3 hours of injury
  - Late treatment (>3hrs after injury) was associated with higher mortality

MATTERs

- Military combat injuries (UK & US) in 896 consecutive trauma admissions
  - Retrospective analysis, 293 received TXA
  - TXA cohort had lower unadjusted mortality (17.4 vs 23.9%) despite higher injury severity scores (25.2 vs 22.5)
  - Those requiring massive transfusion benefitted the most, with improved survival and less coagulopathy
Conclusions on TXA:

- Low cost therapy which improves survival
- Reduces transfusion
- Best if given within 3hrs of injury
- Especially if signs of hyperfibrinolysis (LY30>3% on rTEG)

Dosing: Bolus 1gm (in 100mL) over 10min, followed by 1gm over 8hrs

Prothrombin Complex Concentrate

- Reconstitutable powder of purified, heat-treated, donor pooled human plasma
- Contains Factors II, VII, IX and X and antithrombotic Proteins C & S
- Allows rapid reversal of Warfarin
- When given with Vitamin K, INR reversal is maintained >48hrs.

Advantages of PCC over FFP

- Faster to administer (no thawing)
- Smaller volume (1 mL of reconstituted 4-PCC=10mL FFP)
- More rapid reversal of INR
  - INR <1.4 with in 30 min (in 93% Pts) compared to <10% in FFP group
  - On average INR reversal with FFP took >8hrs to achieve
- Minimal risk of TRALI (lacks antigens)
- Fewer adverse events (death, MI, stroke, heart failure, VTE, peripheral arterial thromboembolism) compared to FFP (9.7% vs 19.5%)
- Most cost-effective (total cost of transfusion)

PCC

- Recommended first line for emergent reversal of Vitamin K antagonists
- May help reverse Factor Xa inhibitors

PCC in trauma?

- High FFP/platelet ratios are not without risk
- Risk of TRALI is highest with FFP transfusion
- Rapid, low volume reversal of factor deficiency
- Available in rural hospitals with limited access to blood products
- Sounds good, right?
Retrospective analysis of 30 patients who received PCC in a variety of settings:
- Warfarin reversal (per hospital protocol)
- Cardiac & Other surgery—both those responding poorly to product transfusion and those with life-threatening bleeds.

Results:
- PCC for non-VKA-related coagulopathy after surgical bleeding
  - Significant decrease in blood products in all pts
  - Partial or complete hemostasis was achieved in 77.8% patients
  - Successful broad use of PCC
  - No thrombotic complications or adverse drug reactions were observed
  - Very small study, retrospective—further investigation warranted

Author’s conclusions
- PCC rapidly and effectively treats coagulopathy after traumatic injury.
- PCC therapy leads to significant correction of INR in all trauma patients, regardless of coumadin use, and concomitant reduction in blood product transfusion.
- PCC should be considered as an effective tool to treat acute coagulopathy of trauma.

Conclusions on PCC
- PCC should be used for rapid reversal of warfarin-induced coagulopathy.
- No high quality prospective trials for it’s use in trauma
- Role for PCC as an adjunct in patients with trauma-induced coagulopathy requiring massive transfusion remains unknown
- Prospective trials are needed
**Recombinant Factor VIIa**
- Binds exposed tissue factor, acts locally at site of injury, accelerates thrombin generation
- "Off-label" use in trauma
- No clinical decrease in mortality (CONTROL)
- Evidence of harm—increased thromboembolic events, particularly coronary arterial thromboembolic events, especially Patients >65
- Should be removed as an adjuvant strategy for massive transfusion protocol

**Fibrinogen Concentrate**
- Fibrinogen plays a pivotal role in coagulation, converted to fibrin, binds platelets to stabilize clot
- 1st factor to reach critical levels during massive hemorrhage
- Hypofibrinogen is strongly associated with poor outcome in trauma
- At <229 mg/dL dramatic rise in mortality in bleeding trauma patient
- FFP (even at high ratios) fails to normalize fibrinogen
- Cryoprecipitate or fibrinogen concentrate are needed to correct hypofibrinogenemia and improve outcome

**Salzburg Trauma Center**
- Nonrandomized comparative study of the use of fibrinogen concentrate in 80 trauma patients to 601 German trauma registry patients
  - Fibrinogen administered based on TEG
  - Fibrinogen group avoided transfusion 29% of time compared to 3%
  - No mortality difference

**4 other small European prospective studies**
- Coagulation was optimized (based on ROTEM)
- Perioperative bleeding was reduced (up to 32%)
- Transfusion requirement was significantly reduced

**Fibrinogen Concentrate**
- Derived from Human donor plasma
- Contains 15mg/mL Fibrinogen compared to 2mg/mL in FFP
- Smaller volume
- Role for administration outside the hospital
- Avoids TRALI and ABO incompatibility

**Fibrinogen Concentrate**
- More studies needed both for efficacy and safety in trauma
- We don’t have a Fibrinogen trigger level (fibrinogen concentration vs TEG (K/angle))
- Recent European guidelines recommend fibrinogen concentrate or Cryo in a bleeding patient with signs of functional fibrinogen deficit or plasma fibrinogen <150–200mg/dL
- Not approved in US yet
References