Department of Anesthesiology
University of Colorado Anschutz Medical Campus

Denver Health
Level One Care for ALL

Trauma Update 2015

part 2

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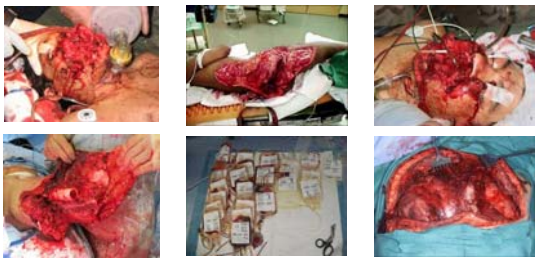


Disclosures:

- 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

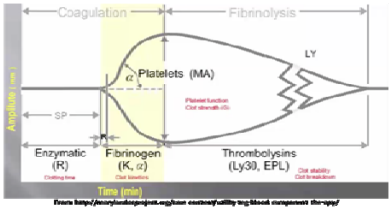
(2)

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)



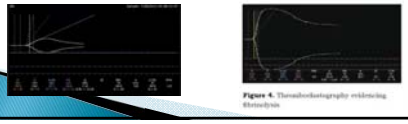
Incidence of Hyperfibrinolysis

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

(7,8)

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

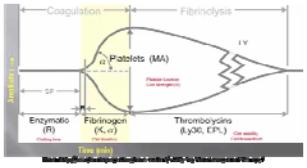


Hyperfibrinolysis in Trauma

- 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

(7,8)

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

(7)

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

(3)

Antifibrinolytics

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

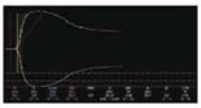


Figure 4. Thromboelastography evidencing fibrinolysis

TXA-CRASH-2

- 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

(3)

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

(3)

MATTERs

- Millitary 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

(4)

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

Anticoagulant or antiplatelet agent	Reversal for Severe or life-threatening bleeding
Warfarin	PCC 25-50units/kg or FFP 2-4units . Also Vitamin K 5-10 mg over 30min
UFH	Protamine 1mg/100units Heparin
LMWH	If last dose <8hr, 1mg Protamine per 100units LMWH If 8-12hrs, 0.5mg Protamine per 100units LMWH
Argatroban/Bivalrudin (IV Direct Thrombin inhibitors)	No reversal agent. Consider FFP, activate MTP, utilize TEG-guided resuscitation
Dabigatran (Oral DTI)	No reversal agent. Consider Hemodialysis Consider FFP. Activate MTP, utilize TEG-guided resuscitation
Factor Xa Inhibitors (fondaparinux, rivaroxaban, apixaban)	No reversal agent. Consider PCC 50units/kg x1 (max 5000units). Activate MTP, utilize TEG-guided resuscitation
ASA,Clopidogrel,Ticagrelor, Prasugrel,Ticlopidine	No reversal agent. Consider DDAVP 0.3mcg/kg IV x1, Platelet transfusion
GIIb/IIIa inhibitors (abciximab, eptifibatide)	Abciximab: platelet transfusion Eptifibatide: platelets less effective, supportive therapy

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.

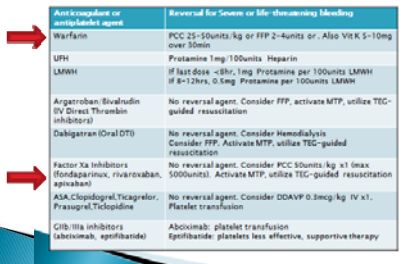
Advantages of PCC over FFP

- 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)

9,10,11

PCC

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



(16,17,18)

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?

Research Open Access

Prothrombin complex concentrate (Beriplex P/N) in severe bleeding: experience in a large tertiary hospital

David Bruce and Tim JC Nokes

Department of Haematology, Derriford Hospital, Brest Road, Plymouth, Devon PL6 8DH, UK

- 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:

- 20 Patients (44%) were <u>not</u> on warfarin
  - INR was reduced significantly from 2.0(+/1 0.6) to 1.2 (+/-0.4)
  - PRBC administration was reduced from 9.8-3.8 units

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.*

Factor IX complex for the correction of traumatic coagulopathy

Bellal Joseph, MD, Albert Amini, MD, Randall S. Friese, MD, Matthew Houdek, BS, Daniel Hays, PharmD, Narong Kulvatunyou, MD, Julie Wynne, MD, Terence O'Keeffe, MD, Rifat Latifi, MD, *and* Peter Rhee, MD, *Tucson, Arizona*

- Retrospective analysis of 4-PCC use at Level 1 trauma center over 2 year period
- Factor IX complex (contains Factors II, VII, IX, X)
- 45 coagulopathic trauma patients (both with and without pre-injury warfarin) treated with 4-PCC
  - 4-PCC requested by the attending for any patient with life-threatening hemorrhage who:
    - Unable to tolerate volume of FFP needed for correction
    - Unable to tolerate the time required for FFP
    - INR refractory to standard FFP doses
    - Patients with continued coagulopathy and hemorrhage despite massive resuscitation
- Off label use of 4-PCC

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

(19)

Salzberg 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

(20)

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

(20-24)

4 other small European prospective studies

- Coagulation was optimized (based on ROTEM)
- Perioperative bleeding was reduced (up to 32%)
- Transfusion requirement was significantly reduced

(20,21,22,23)

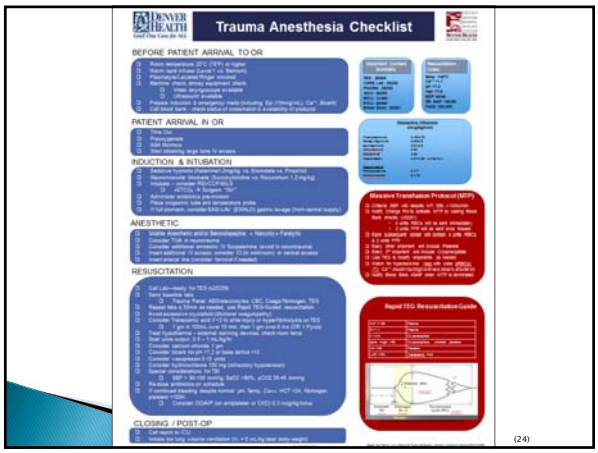
Fibrinogen concentrate

- 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

(20)

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



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