Resuscitation Update

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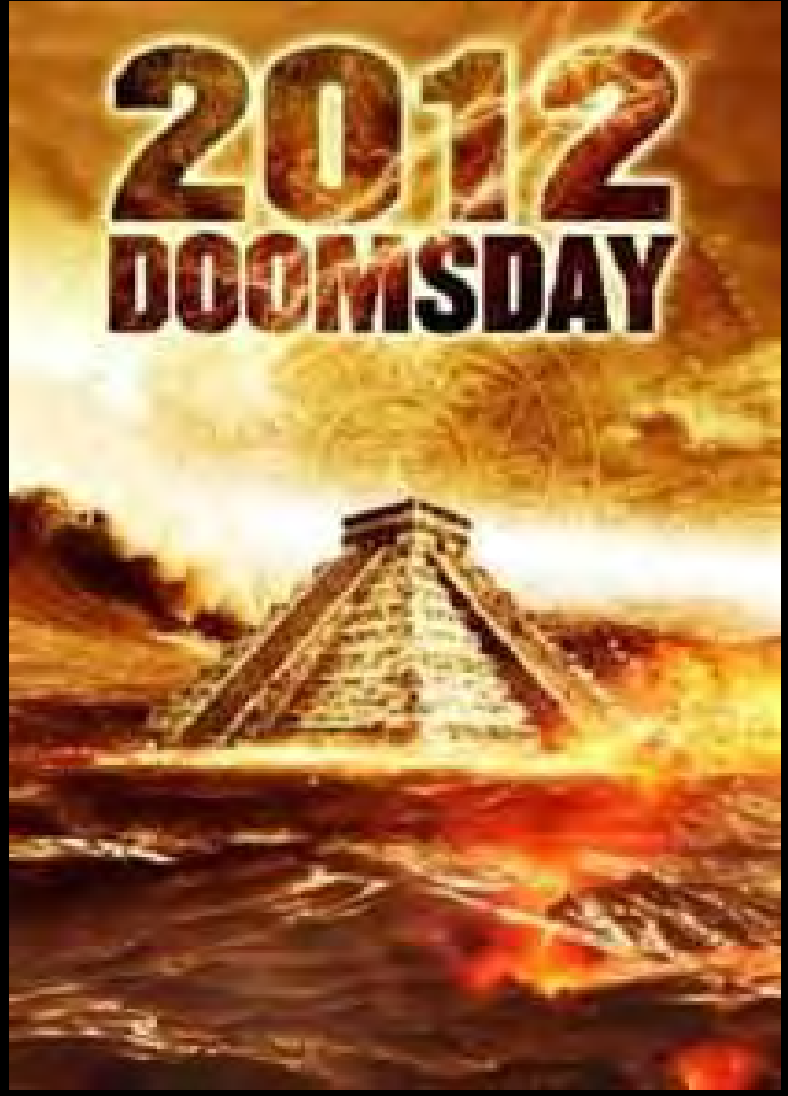
2009 Recommendations

- Where we last left off in 2009
- Many indicators to help monitor the progression of the resuscitation
- Use of Massive Transfusion Protocols reduces mortality
- Early FFP if the patient is demonstrating signs of instability and requiring large volumes of blood transfusion
- FFP:PRBC transfusion ratios similar to 1:1 are the best ratios



Not the end of the world.
However….

2012 Resuscitation Update

- New FFP: PRBC ratio recommendations
- Stopping hemorrhage (anti-fibrinolytic)
  - Tranexamic Acid
- Treatment of Coagulopathy
  - Factor VIIa
  - Prothrombin Complex Concentrates (PCC)
  - Factor Eight Inhibitor Bypassing Activity (FEIBA)

2012 Resuscitation Update

- Treatment of Coagulopathy (cont'd)
  - Freeze Dried Plasma

FFP:PRBC ratio
(How do we prepare?)

The Best Deal

- WHOLE BLOOD (<24 hrs old)
  - Hct 38 to 50%, Platelet count of 150,000 to 400,000, full coagulation function, fibrinogen 1500 mg
- 1 unit PRBC + 1 unit FFP + 1 unit of platelets + 10 pack cryoprecipitate
  - Hct 29%, Platelet count 87,000, 65% clotting ability, fibrinogen 750 mg

Damage Control Resuscitation

- Combat Literature from the experiences of wars in Iraq and Afghanistan
  - Tolerance of hypotension SBP=90
  - Minimal fluid as long as radial pulse and normal mental status
  - Limit clothing removal to injured areas to reduce hypothermia
  - Prevent secondary acidosis
  - Survival benefit with FFP:PRBC ratio 1:1

Damage Control Resuscitation

- Combat Literature from the experiences of wars in Iraq and Afghanistan
  - Replaces losses with appropriate losses. Blood for blood
  - Routine thawed FFP each morning
  - Identification of those patients who need massive transfusion – penetrating injuries

Massive transfusion protocols reduce incidence of organ failure and complications

Cotton, BA et al. J Trauma 2009 Jan;66(1):41-48.

- Using a TEP 2:3 FFP:PRBC, 1:5 Platelets:PRBC and comparing to a non-utilization period
- Reduction in multiorgan failure (Cardiac, Hepatic). No difference in resp and renal failure
- Reduction in infectious complications (VAP, sepsis)
- Increase in ventilator free days
- Higher 30 day survival

TEP = Transfusion Exsanguination Protocol

Massive transfusion protocols reduce incidence of organ failure and complications

Cotton, BA et al. (cont'd)

- Shorter Length of Stay
- Patients with abdominal compartment syndrome were 80% more likely to be closed primarily within 7 days

>1:1.5 FFP:PRBC transfusion ratio is associated with lower mortality

Sperry, JL et al. J Trauma 2008 Nov;65(5):986-93.

- Prospective Cohort Study of 415/1036 blunt trauma patients who received > 8 units PRBC in first 12 hours
- Patients separated by ratio 1:1.5 FFP:PRBC
- FFP:PRBC ratio of > 1:1.5 was associated with a 52% lower risk of mortality
- However also associated with 2 fold risk of ARDS

1:3 ratio of FFP:PRBC in massively transfused patients is maximum benefit

Teixeira PG et al J Trauma 2009 March 66(3) 693-697

- 6 year retrospective study 4,241/25,599 patients
- 484 patients were massively tranfused (>10 units PRBC during first 24 hours
- 101 patients excluded due to severe head trauma
- Ratios examined: <1:8, >1:8 and < 1:3, >1:3 and <1:2, >1.2 (low, medium, high, highest)

Teixeira PG et. al. **J Trauma**. 2009 March 66(3) 693-697

1:3 ratio of FFP:PRBC in massively transfused patients is maximum benefit

Teixeira PG et al (cont'd)

- Higher FFP:PRBC ratios is an independent predictor of survival
- Maximum survival benefit ratio seems to be up to 1:3

Increased use of plasma in nonmassively transfused trauma patients is associated with increased complications

Inaba K et al. J Am Coll Surg. 2010 Jun;210(6): 957-965. Epub 2010

- 5 yr. retrospective study 1716/1933 patients received a nonmassive transfusion (less than 10 units PRBC in the first 12 hrs of admission)
- Matched 284 patients who received plasma vs. those who did not
- Exclusion of 31 early deaths

Increased use of plasma in nonmassively transfused trauma patients is associated with increased complications

Inaba K et al. (cont'd)

- Patients that received > 6 units FFP and increased incidence of pneumonia and sepsis (4x), MODS (6x), and ARDS (12x)
- No improvement in survival regardless of the FFP:PRBC ratio

PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) Study.

- Holcomb JB et al. Arch Surg 2012 Oct 15:1-10 [Epub ahead of print]
  - 10 major civilian trauma centers
  - Prospective observational study of severely injured transfused trauma patients.
  - 12,561 trauma admissions and enrolled 1245 patients who received one or more blood transfusions within 6h of Emergency Department (ED) admission. A total of 297 massive transfusions were observed

Experience from the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) Study.

- Holcomb JB et al. (cont'd)

- Preliminary Evaluation of the data
  - Patients who had survived 30 minutes after admission
  - Received at least 1 unit PRBC with 6 hours of admission
  - Received at least 3 total units (PRBC, plasma, or platelets) in 24 hour

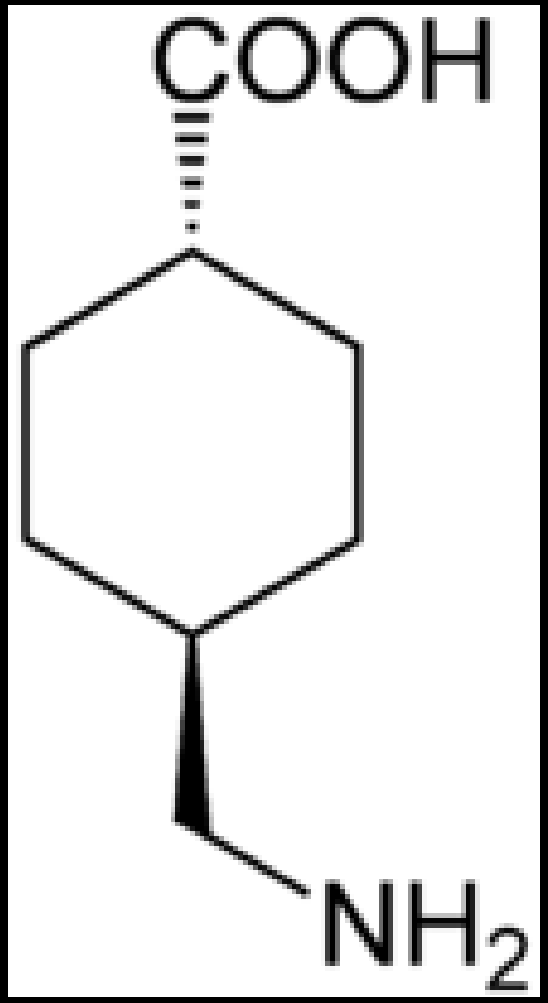
Experience from the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) Study.

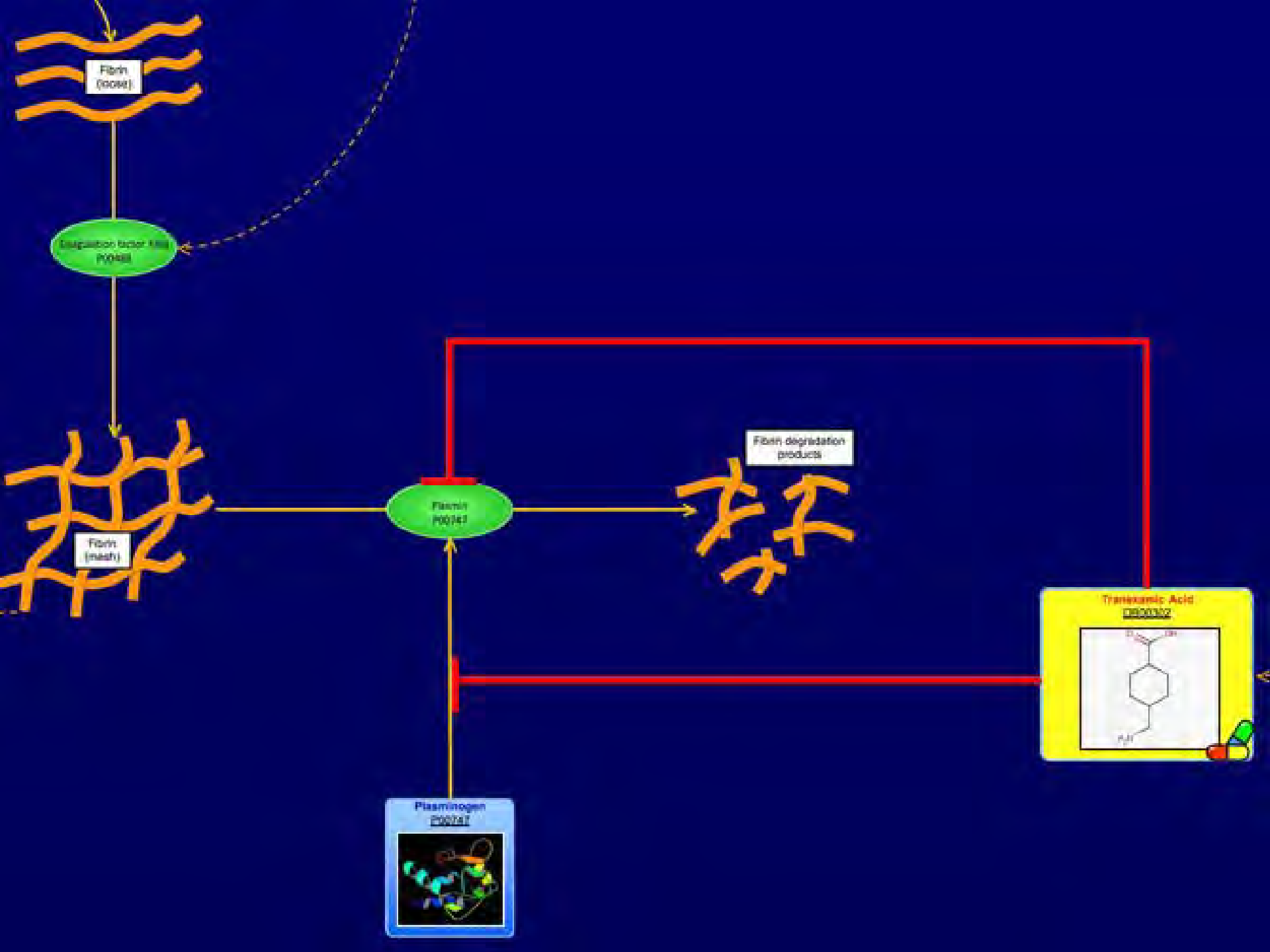
- Holcomb JB et al. (cont'd)
- Results
  - Increased ratios of FFP:PRBC or Platelets:PRBC associated with a decreased 6 hour mortality
  - In the first 6 hrs, ratios < 1:2 had 3 to 4 times higher mortality than those with ratios 1:1 or higher
  - The risk of death by day 30 was not associated with the ratios of plasma or platelet

Tranexamic Acid and the CRASH-2 Studies

Tranexamic acid

- Synthetic derived from the amino acid lysine
- Inhibits fibrinolysis by blocking lysine binding sites for plasminogen
- Shown to reduce blood transfusion in elective surgery by 1/3 in review of 53 studies
- No reduction in mortality




Fibrin
(soluble)
Coagulation factor XIIIa
P00488
Fibrin
(mesh)
Plasmin
P00747
Fibrin degradation
products
Tranexamic Acid
DB00302
Plasminogen
P00747

CRASH-2

- Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage
  - Multinational study involving 274 hospitals in 40 countries.
  - 20,211 patients enrolled
  - Study the effect of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage
  - Definition of sign. hem. was SBP <90 or HR > 110, those at risk for significant hemorrhage, within 8 hours of injury

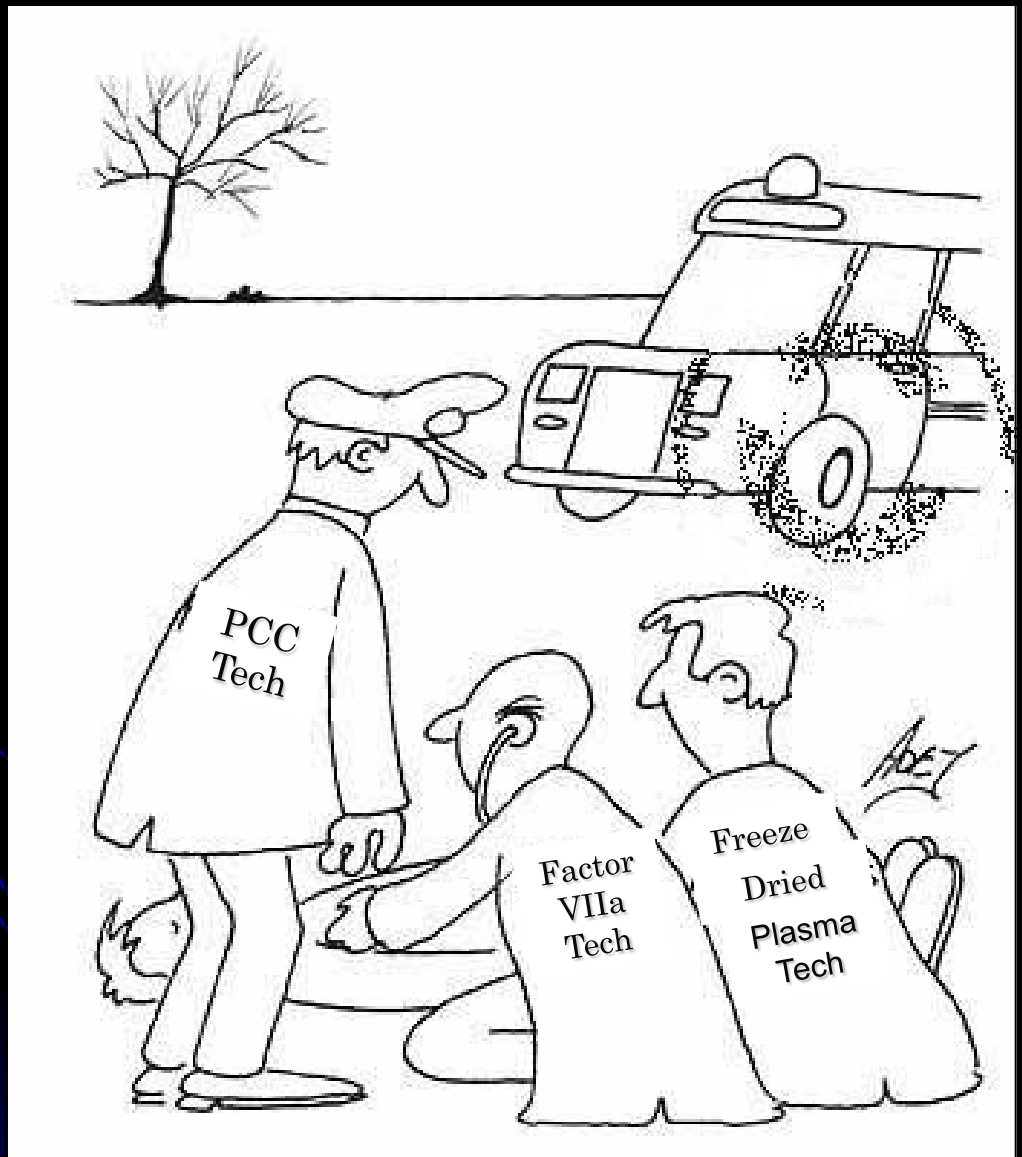
CRASH-2

- Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage
  - TXA 1gm in 10 minutes for the first 8 hours. Followed by infusion 1 gm over 8 hours.
  - Results
  - 10% Reduction of mortality from bleeding
    - (1463 patients died in TXA group versus 1613 patients died in placebo group)
  - No difference in blood used by both groups

CRASH-2

- Further subset analysis studies
  - Benefits were best at 1 hour post injury and up to 3 hours
  - After 3 hours, mortality increases
  - Overall cost to treat 1000 patients in the United Kingdom was $30,830
  - In severe TBI no harm but no benefit

Treatment of Coagulopathy



Recombinant Factor VIIa

Recombinant Factor VIIa

- Clotting Factor manufactured by the Novo Nordisk company
  - Indications in use
    - Hemophiliacs with antibodies to factor VIII
    - Compassionate use in trauma and uncontrolled hemorrhage
  - Caution as may cause thromboembolic events
  - Caution as is expensive $1 per mcg

Recombinant Factor VIIa

- Dosing (per OSF Pharmacy)
  - First Dose 60 mcg/kg IV over 2 to 5 minutes any IV may be used
  - Second Dose at 120 mcg/kg in 2 hours if bleeding continues and there was response with the first dose
  - Third Dose at 120 mcg/kg

Recombinant Factor VIIa

- Duchesne, JC et al. Am Surg 2008 Dec;74(12):1159-1165. “Current evidence based guidelines for factor VIIa use in trauma:the good, the bad, and the ugly.”
  - Review of 118 articles
  - Level I evidence only in blunt trauma. Boffard et al. J Trauma 2005;59:8-18 (After 8 units PRBC)
  - Doses used were 200mcg/kg + 100mcg/kg + 100mcg/kg
  - Demonstrated reduction in PRBC transfused

Recombinant Factor VIIa

- Duchesne, JC et al.
  - Class II evidence in three studies demonstrated reduction in blood transfusion
  - Additionally one study demonstrated reduction in 24 hr and 30 day mortality
  - High dose still recommended
  - Class III evidence demonstrated earlier administration was better
  - Also some evidence to suggest lower efficacious dosing

TABLE 1. *Evidence Based Table*

	Author	Study Outcome
Class I	Boffard et al. 2005[18]	Three doses of rFVIIa (200, 100, 100μm/kg) with first dose given after transfusion of eight RBC units and additional doses at 1 and 3 hours later resulted in: 1) a statistically significant reduction in RBC units used by 2.6 in blunt trauma 2) significant reduction in the need for massive transfusion in blunt trauma 3) similar although statistically insignificant trends were also noted in penetrating trauma 4) no difference in adverse events among treatment groups 5) trend towards decreased mortality

Recombinant Factor VIIa

- Short half-life (1.7 to 3.1 hours)
- Need additional anticoagulation reversal products due to the short half-life
- Most studies included FFP and Vitamin K usage
- CONTROL trial

CONTROL trial to evaluate Factor VIIa

Hauser CJ et al. J Trauma 2010 Sep;69(3):489-500.

- First Phase 3 randomized clinical trial
- Patients who bled 4 to 8 red blood cell units within 12 hours of injury and were still bleeding despite strict damage control resuscitation and operative management were enrolled
- Patients were assigned to rFVIIa (200 μg/kg initially; 100 μg/kg at 1 hour and 3 hours) or placebo.

CONTROL trial to evaluate Factor VIIa was terminated early due to futility

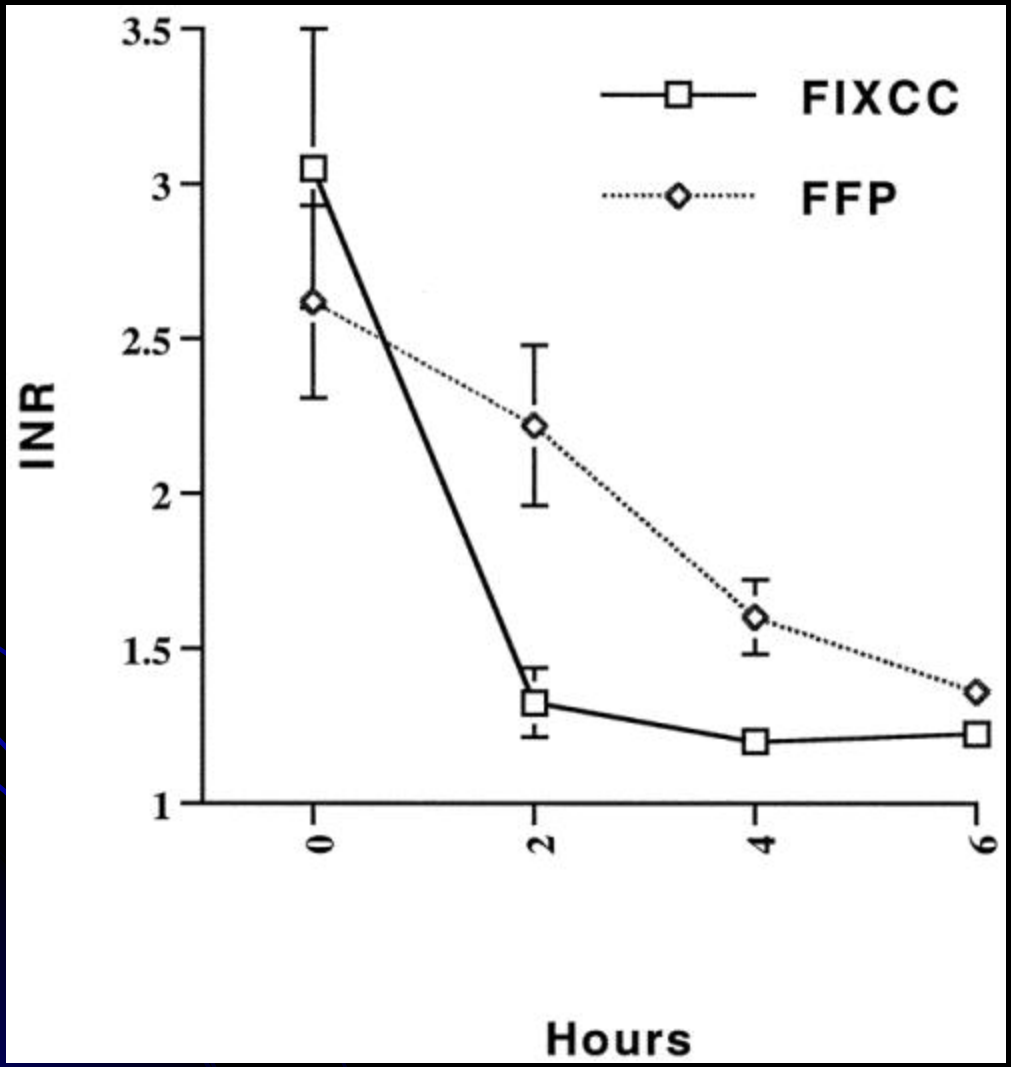
- Study was stopped at 573 of 1502 planned patients because of futility analysis
  - Mortality was 11.0% (rFVIIa) versus 10.7% (placebo)
  - The study would not have been able to demonstrate survival benefit if continued
- rFVIIa reduced blood product use and there was no increased in thrombotic events

Prothrombin Complex Concentrates (PCC)

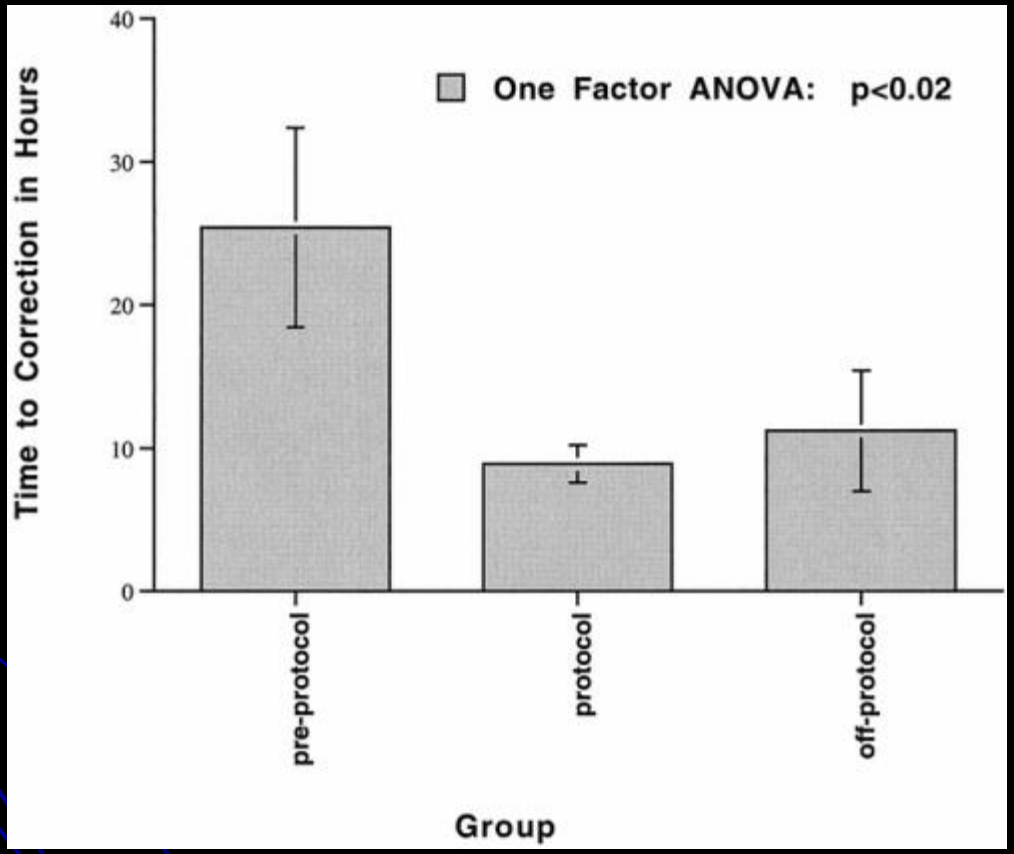
- Originally created to treat Hemophilia B (Factor IX deficiency)
- Contains Factors II, VII, IX, and X as well as Proteins C and S
- More safe than Fresh Frozen Plasma (FFP) due to additional purification processes
- Smaller volume than FFP

PCC vs. FFP

- Boulis NM et al 1999
  - Prospective RCT evaluating warfarin associated intracranial hemorrhage
  - 13 patients total
  - 8 received standard FFP therapy
  - 5 received FFP + PCC
- Results
  - Faster correction of INR.
  - Higher complication rate observed in FFP only group
  - No difference in outcomes



Boulis NM et al Neurosurgery 1999 Nov;45(5):1113-1118



Boulis NM et al Neurosurgery 1999 Nov;45(5):1113-1118

PCC vs. FFP

- Cartmill M et al 2000
  - 12 patients
  - 6 treated with 4 units FFP and vitamin K
  - 6 treated with 50 mcg/kg PCC and vitamin K

- Results
  - More complete correction of INR (1.3 vs 2.3)
  - Faster correction of INR with PCC group

Prothrombin Complex Concentrates (PCC)

- Non-Active agents
  - 3 Factor
  - 4 Factor
- Active agents
  - Factor Eight Inhibitor Bypassing Activity

Nonactive PCC

- 3 Factor (available in the United States)
  - Contains mostly Factors II, IX, and X
  - Has reduced amounts of Factor VII
  - Recent studies recommend addition of Vitamin K or FFP

Nonactive PCC

- 4 Factor (not approved in United States)
  - More complete – Factors II, VII, IX, and X

Factor Eight Inhibitor Bypassing Activity (FEIBA)

FEIBA

- Activated PCC
- Been around for 30 years
- Cost about $1.50 per IU

FFP vs. FEIBA

- Wójcik C et al 2009
  - Retrospective review
  - 72 patients received FEIBA compared to 69 patients treated with FFP
  - FEIBA dosing varied by INR
    - INR <5 – Received 500 units
    - INR >5 – Received 1000 units
  - Aim to correct INR ≤ 1.4

PHYSICIAN'S ORDERS
DEACONESS HOSPITAL, INC

(PATIENT LABEL)

PROTHROMBIN COMPLEX CONCENTRATE (PCC)
FOR ACUTE REVERSAL OF ORAL ANTICOAGULATION

Date	Hour	PHYSICIAN'S ORDERS
		For the emergent reversal of life-threatening bleeding in patients receiving oral anticoagulation therapy
		Contraindications • Bleeding episodes resulting from coagulation factor deficiencies • Disseminated intravascular coagulation (DIC) • Fibrinolysis • Normal coagulation mechanism **Warnings** • Risk of viral infection from human plasma product • Caution in hepatic disease • Use in newborns, non-hemophilic patients, or those with thrombosis risk factors
		Prothrombin Complex Concentrate (PCC) Dosing for Reversal of Oral Anticoagulation ☐ INR is less than 5 • Give 500 units of PCC IV now over 10 minutes • Recheck INR in 30 minutes: if greater than 1.5, contact Physician to determine if another 500 units of PCC is needed ☐ INR is greater than 5 • Give 1000 units of PCC IV now over 15 minutes • Recheck INR in 30 minutes: if greater than 1.5, contact Physician to determine if another 500 units of PCC is needed ***Do not exceed a rate of 2 units/kg/minute**
		Vitamin K (Phytonadione) ☑ Give vitamin K 10 mg / D_5W 50 mL IV once now over 30 minutes
		Monitoring ☑ Check INR 30 minutes after PCC infusion ends and again in _____ hours ☑ Signs of a thromboembolic event
		_____ PHYSICIAN SIGNATURE
		PHYSICIAN'S ORDERS

Approved by Pharmacy & Therapeutics Committee May 2007
Approved by Medical Executive Committee June 2007

F-5880* (6-07)

Wójcik, Cezary et al Int J Emerg Med 2009. 2: 217-225.

FFP vs. FEIBA

- Wójcik C et al 2009
  - Results
  - INR was corrected faster than with FFP
    (2 hours vs. 25.2 hours)
  - Incidence of thrombotic event was no different than with nonactivated PCCs (7%)
  - No change in mortality

FFP vs. FEIBA

Measured parameter	FEIBA			FFP			p value
	INR <5 (n = 51)	INR ≥5 (n = 21)	Total (n = 72)	INR <5 (n = 54)	INR ≥5 (n = 15)	Total (n = 69)	
Age	75(45–90)	76(51–95)	75(45–95)	78(32–91)	77(36–88)	77(32–91)	0.479
Sex	65.3%M 34.7%F	52.2%M 47.8%F	61.1%M 38.9%F	44.4%M 55.6%F	46.7%M 53.3%F	44.9%M 55.1%F	0.079 §
Median INR at admission	2.6(1.2–4.9)	12.8(5.0-∞)	3.3(1.2-∞)	2.5(1.3–4.8)	7.4(5-∞)	2.9(1.3-∞)	0.104
% of patients with INR <5 at admission	100%	0%	70.8%	100%	0%	78.3%	0.207
Median INR after drug administration	1.4(1.1–3.2)	1.5(1.1-∞)	1.5(1.1-∞)	1.6(1.0–3.2)	2.0(1.5–4.8)	1.6(1.0–4.8)	0.046
% of patients with INR ≤1.4 following drug administration	51.1%	42.9%	50.7%	28.2%	7.7%	33.3%	0.017 §
Median INR drop	1.2(-0.1–3.4)	11.3(0-∞)	1.8(-0.1-∞)	0.8(0–3.2)	11.6(1.2-∞)	1.0(0-∞)	0.014
Mean hemoglobin at admission (g/dl)	12.0 ± 3.5	9.3 ± 3.3	11.1 ± 3.7	11.1 ± 2.8	10.9 ± 2.6	11.1 ± 2.8	0.870
Dose administered (units)*	504 ± 19	999 ± 40	662 ± 234	2(1–11)	4(2–5)	2(1–11)	n/a
% of patients with initial 1,000 units FEIBA dose	0%	100%	31.9%	n/a	n/a	n/a	n/a
% of patients with additional drug dose	16.3%	21.2%	18.1%	20.4%	13.3%	18.8%	0.923 §
Median time from drug administration to measurement of INR <1.4 (h)	2.0(0-∞)	4.8(0-∞)	2.0(0-∞)	23.7(2-∞)	29.2(12.5–50.9)	25.2(2-∞)	0.006
% of patients with ICH	46.9%	21.7%	38.9%	9.3%	26.7%	13.0%	<0.001 §
Median length of hospital stay (days)	6(1–20)	6(1–15)	6(1–20)	6(1–64)	5(1–17)	6(1–64)	0.521
Survival	79.6%	73.9%	77.8%	88.9%	85.7%	88.2%	0.545 §

Int J Emerg Med

Wójcik, Cezary et al Int J Emerg Med 2009. 2: 217-225.

Freeze Dried Plasma (FDP)

- In USA, still in Research and Development and will not be available till 2015 – 2017
- German Red Cross has been using this
- Has been used by the French Military Health Service

Freeze Dried Plasma (FDP)

- Martinaud C et al 2011
- Prospective eval of FDP in Afghanistan
  - Demonstrated significant reduction in PT (decrease from 20 +/- 9.1 to 16.7 +/- 4 seconds)
  - Incomplete dataset
  - Not compared to FFP (fresh frozen plasma)
  - Unclear the significance of this study

Freeze Dried Plasma (FDP)

- Shuja F et al 2008
- Comparison of FFP to FDP
  - Porcine model
  - Induced femur fracture, grade V liver laceration, and hemorrhagic shock
  - FDP and FFP equally effective in correcting INR

Summary of Coagulation Treatments Available

Vitamin K dependent coagulation factors	Recombinant Factor VIIa	Fresh Frozen Plasma	Three -Factor Prothrombin Complex Concentrate	Four -Factor Prothrombin Complex Concentrate	Factor Eight Inhibitor Bypass Activity
X		✓	✓	✓	✓
IX			✓	✓	✓
VII	✓	✓		✓	✓
II		✓	✓	✓	✓

Zareh, Meena et al . West J Emerg Med 2011. November; 12(4) 386-392.

Conclusions

INR	Recommendation
<5	Hold 1 dose or lower dose of warfarin
5.0–<9	Add 1–2.5 mg of oral vitamin K
>9 (no bleeding)	Hold warfarin and give 2.5–5.0 mg of oral vitamin K
Any major bleeding	Hold warfarin and give 10 mg intravenous vitamin K in addition to fresh frozen plasma, Prothrombin Complex Concentrate, or recombinant Factor VIIa

INR, international normalized ratio.

The American College of Chest Physicians guideline for the reversal of anticoagulation therapy (8th ed.)

Conclusions

- Unstable trauma patient
  - Tranexamic Acid given in the first 3 hours of injury for patients who are bleeding and unstable
  - 3 factor PCC or FEIBA or Factor VIIa + vitamin K and FFP at the hospital along with PRBCs

Conclusions

- Stable trauma patient
  - Treat as necessary
  - FFP + Vitamin K + PRBCs
  - FFP:PRBC ratio not to exceed 1:3

Conclusions

And hopefully by then we will have 4- factor PCC and FDP

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