Acute Intracerebral Hemorrhage: What is the Optimal Therapy in the Anticoagulated Patient?

Chris A. Ghaemmaghami, MD
Associate Professor of Emergency Medicine
University of Virginia
USA

Acknowledgement:

This session was initially developed by

Mark I. Langdorf, MD, MHPE
Professor and Chair, Department of Emergency Medicine
University of California, Irvine

Disclosure

- None

Session Objectives

- Describe the current state of knowledge regarding reversal of anticoagulation in patients with acute intracranial hemorrhage
- Focus on warfarin reversal
- Review outcomes of activated Factor VII and prothrombin concentrate complex clinical trials

Clinical Questions

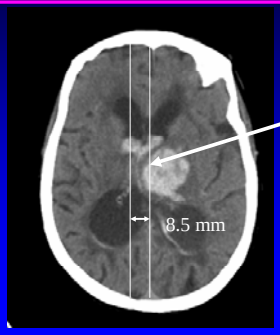
- What is the rationale for using warfarin anticoagulation?
- What risk does this pose?
- What options are available to reverse anticoagulation?
- How fast do they work?
- What is the risk of pro-coagulant complications?
- Does reduction in bleeding lead to better functional outcome or reduce mortality?

Case Study: Acutely Unresponsive

- 91 yo with HTN, dementia, old ischemic strokes
- Coumadin for history of atrial fibrillation
- 208/123, HR 76, Temp 37.2 C, RR 12
- Pupils 3mm and sluggish, conjugate deviation to right
- GCS 10-11, RUE motor 2/5, LUE 4/5
- Hgb 14.9, platelets 270K, INR 3.1

Sudden Loss of Consciousness

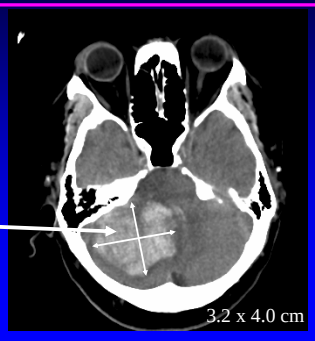
Sudden Loss of Consciousness



Case 2: Sudden LOC

- 71 yo right handed Indian male with sudden LOC, vomiting, and 10 minutes of seizure activity
- On Naproxen for arthritis
- Vitals BP 200/90, HR 87, RR 14, Temp 36.7 C
- GCS 6, pupils 1mm and nonreactive bilaterally
- Flexure posturing R > L, toes equivocal
- No dolls eyes, but corneal and gag preserved
- Hgb 11, platelets 236K, INR 1.03, PTT normal

Sudden Loss of Consciousness



Sudden Loss of Consciousness

ICH: Scope of the Problem

- 10-15% of first-ever strokes
- 30 day mortality 35-52%
- Only 20% are functionally independent at 6 months
- Hematoma growth associated with five-fold increase in clinical deterioration, poor outcome and death

Silva Y, Leira R, Stroke 2005;86-91

Why Use Warfarin at all?

- Atrial fibrillation: risk of embolic stroke 5% per year

- Rises to 12% per year with history of prior stroke
- 4% per year with prosthetic mechanical valves

Warfarin Risk

- ICH: 0.3-0.6% per patient year
- 6-23% of all ICH are on warfarin
- 8-10,000/year in the USA
- OR of 6.2 for hematoma expansion and continues longer
- ICH risk doubles for each 0.5 INR unit > 4.5

Flibotte JJ, Hagan N, Neurology 2004, 1059-64
Rosand J, Eckman MH, Arch IM, 2004, 880-4
Aguilar MI, Hart RG, Mayo Clin Proc, 2007

Anticoagulation Reversal for ICH

Management option	Time to anticoagulation reversal	Comments and cautions
Discontinuing warfarin therapy	5-14 d	
Vitamin K†	6-24 h to correct the INR	Replacement of factors IX and X takes longer than 24 hours, risk of anaphylaxis with intravenous injection, warfarin resistance in higher doses up to 1 wk
Fresh frozen plasma	3-6 h for infusion, typically 12-32 h for reversal	Volume (2-4 L to normalize INR) can be prohibitive
Prothrombin complex concentrate	15 min after 10-min to 1-h infusion	Limited availability, cost, variable cofactor content based on manufacturer, potentially prothrombotic
Factor VIIa concentrate	15 min after bolus infusion	Short half-life, cost, potentially prothrombotic, uncertain safety

*INR = international normalized ratio.
†A total of 10 mg intravenously by slow infusion throughout 10 minutes.

Aguilar MI, Hart RG, Mayo Clin Proc, 2007

American College of Chest Physicians Guidelines, 2004

Condition	Description
INR < 5 No significant bleeding	Lower or omit next warfarin dose
INR >5 but <9 No significant bleeding	Omit next 1 or 2 warfarin doses Vitamin K up to 5mg po if increased bleeding risk
INR >9 No significant bleeding	Hold warfarin until theraputic Vitamin K 5-10mg po
Any INR Serious bleeding	Hold warfarin Vitamin K 5-10mg IV FFP or PCC
Any INR Life-threatening bleeding	Hold warfarin Vitamin K 5-10mg IV PCC or Factor VIIa

Anticoagulation Reversal Options

- Vitamin K
- Fresh frozen plasma
- Platelet tranfusion
- rFVIIa
- Prothrombin complex concentrate
- Tranexamic acid
- Desmopressin

Vitamin K_1

- Takes at least 6 hours to normalize INR, 24 hours for full effect
- Given 10 mg IV (small risk of anaphylaxis) or subq
- Necessary but not sufficient
- AHA/ASA Class I, Level of evidence B

Reversal of Heparin

- Protamine sulfate
- 1 mg per 100 units of heparin if heparin stopped just prior to protamine
- Reduced dose the longer the heparin has been off (0.25-0.375 mg/100 units after 2 hours)
- Slow IV < 5 mg/min to avoid hypotension
- AHA/ASA Class I recommendation, Level of evidence B

Fresh Frozen Plasma

- Replenishes vitamin K dependent clotting factors inhibited by warfarin
- 12-20 ml/kg = 1400ml = 6 units
- Volume overload and time
- Unpredictable factor levels and low factor IX
- "impractical"

Activated Factor VII

- rFVIIa approved for hemophilia bleeding
- Mechanism:
  - Interacts with tissue factor and stimulates thrombin generation directly
  - Activates factor X on platelet surface which also activates thrombin
  - Converts fibrinogen to fibrin = stable clot
- Half life of 2.6 hours


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

- Phase II dose finding trial
- 399 patients diagnosed with ICH within 3 hrs
- Primary outcome: change in hematoma volume at 24 hrs
- Clinical outcomes at 90 days

Mayer SA, Brun NC, NEJM, 2005

Activated Factor VIIa Trial Outcomes

- Hematoma growth: 29% placebo vs 16, 14, 11% in three treatment groups (p = .01)
- 69% in placebo group dead or severely disabled vs. 53% in three treatment groups (p = .004, 95% CI 4.5-25%)
- Serious clots elsewhere: 7% vs 2% placebo (p= .12)

Mayer SA, Brun NC, NEJM, 2005, 777-85

Problems with aFVIIa Trial

- Industry sponsored
- Excluded:
  - anticoagulated patients
  - coagulopathy patients
  - Patients with known thrombo-embolic disease
- Placebo group had more brainstem strokes, more men, lower GCS at entry = worse outcome
- Not powered to detect increase in thrombotic events (2 vs. 7%)
- 2/9 thrombotic strokes fatal
- Other series: 10% symptomatic MI vs. 1%

Mayer SA, Brun NC, NEJM, 2005
Greenberg SM, Neurology 2006

AHA/ASA Guideline for Activated Factor VIIa Use: 2007

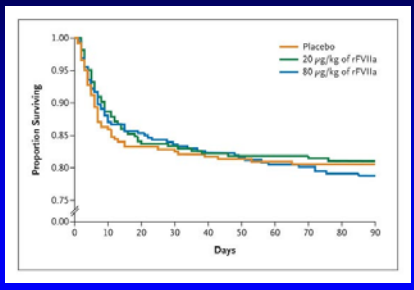
- "has shown promise"
- "efficacy and safety must be confirmed in phase III trials before it can be recommended outside of clinical trials"
- Class IIb recommendation, Level of evidence B

FAST Trial Results

- Randomized placebo-controlled trial of 821 patients
- ICH within 3 hours onset
- Outcome: Death or severe disability at 90 days
- Reduced hematoma growth
  - 26% growth with placebo
  - 18% with lower dose
  - 11% higher dose (p=0<.004 for the higher dose)

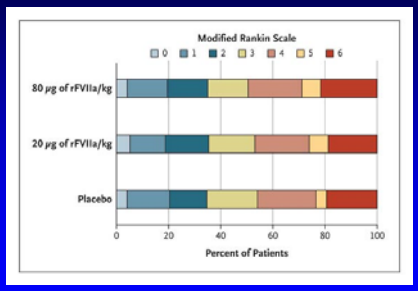
Mayer et al. NEJM 2008; 358 (20): 2127

FAST Trial Results



Mayer et al. NEJM 2008; 358 (20): 2127

FAST Trial Results



Mayer et al. NEJM 2008; 358 (20): 2127

FAST Trial Results

Acute Thrombotic Events

Arterial Thrombosis	rFVIIa 20 mcg/kg	rFVIIa 80 mcg/kg	placebo
Acute MI	5%	8%	4%
Cerebral Infarction	4%	5%	3%

Mayer et al. NEJM 2008; 358 (20): 2127

FAST Trial Results

- No significant effect on mortality/disability:
  - 24% controls
  - 26% low dose
  - 29% higher dose
- Why? 2005 placebo group did poorly (29% mortality vs. 19% in the FAST trial)
  - Lower GCS, more brainstem bleeds, more intraventricular bleeds, more men
- Surrogate markers are often misleading

Mayer et al. NEJM 2008; 358 (20): 2127

rFVIIa Utilization

Broader Literature on rFVIIa

- Cochrane Review April, 2007
- Non-hemophiliac population search
- Randomized placebo-controlled
- 13 trials
  - 6 (n=724) for prevention
  - 7 (n= 1214) for treatment
- No differences between groups that could not be due to chance

Stanworth SJ, Birchall J, Cochrane Database of Systematic Reviewe, 2007, Issue 2

rFVIIa in Warfarin-associated ICH

- 4 studies of 27 total patients
- Two trials (n=14) also gave FFP and Vitamin K
- May not reverse coagulopathy of all vit K dependent factors
- No studies of rFVIIa vs. Prothrombin Factor IX concentrates in ICH

Prothrombin Complex Concentrate

- Beriplex P/N, Proplex-T, Autoplex T, FEIBA, Bebulin, Profilnine HT, Konyne 80
- Factor IX complex concentrate has high levels of II, VII, and X
- 8 Studies of 107 patients with warfarin-associated ICH
- Not widely available in the US
- Restricted to hematology?
- AHA/ASA Class IIb recommendations

Aguilar MI, Hart RG, Mayo Clin Proc, 2007

Prothrombin Complex Concentrate

- Dose based on Factor IX component
- 25-50 IU/kg total dose = 3500 IU
- First 500-1000 IU at 100 IU/min max over 10 min, then 25 IU/min
- Goal INR: 1.2
- Check after 30 minutes
- Cost $1500 per dose
- Repeat if necessary

Aguilar MI, Hart RG, Mayo Clin Proc, 2007

Beriplex P/N

- Beriplex® P/N is a highly purified, lyophilized human plasma fraction containing balanced amounts of the coagulation factors of the prothrombin complex (II, VII, IX and X) and of protein C and protein S.

Prothrombin Complex Concentrate

- 58 patients needing emergent surgery treated, median age 75
- 25-50 units/kg of PCC
- INR measured before and < 1 hr after treatment
- Median pretreatment INR 3.8 (1.4-52.8)
- < 1hr later median INR was 1.3 (0.9-5.7)
- Only two patients with INR > 2.0
- All got Vitamin K too, and 50% got FFP

Lankiewicz MW, Hays J, J Thromb Haemost, 2006.

ORIGINAL ARTICLE

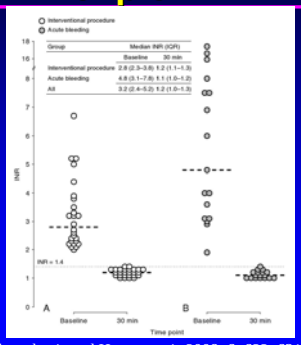
Prothrombin complex concentrate (Beriplex® P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial

I. PABINGER,* B. BRENNER,† U. KALINA,‡ S. KNAUB,‡ A. NAGY§ and H. OSTERMANN¶ FOR THE BERIPLEX® P/N ANTICOAGULATION REVERSAL STUDY GROUP

- Open, uncontrolled, multinational phase III study
- 26 patients who required emergency surgery and 17 who had acute bleeding (43 total) were treated with Beriplex® P/N based on baseline INR.
- A rapid correction of INR (≤ 1.3) was achieved in 40 of the 43 patients (95%). The remaining 3 patients had an INR of 1.4.
- There was good/satisfactory hemostatic efficacy of 98% as assessed by the investigator.

Journal of Thrombosis and Haemostasis 2008; 6: 622–631

Beriplex P/N



Journal of Thrombosis and Haemostasis 2008; 6: 622–631

Prothrombin Complex Concentrate

- Thrombosis 4/57 pts (7%) where this was reported
- Early mortality of 24% (15/64) where this was reported
- Overall risk of thrombosis not clear
- "Probably safe"

Aguilar MI, Hart RG, Mayo Clin Proc, 2007

Tranexamic Acid

- Trade name Cyclokapron (US) or Transamin (Asia)
- Antifibrinolytic competitively inhibits conversion of plasminogen to plasmin which, in turn, degrades fibrin
- Fibrin basic to blood clot formation and stability
- 8 times the activity of an ε-aminoacaproic acid (Amicar)

Tranexamic Acid

- 2004 Cochrane review of 89 RCTs/8,580 patients
  - elective surgery: 74 cardiac, 8 ortho, 4 liver, 3 vascular
- Reduced patients needing transfusion by 1/3
- Reduced transfusion one unit on average
- Cut need for further surgery by 50%
- Mortality reduction RR = 0.85 (95% CI 0.63–1.14)
- 25 mg/kg IV
- 15 ongoing trials at clinicaltrials.gov
- None with ICH or warfarin

Henry DA, Moxey AJ, Cochrane Database Syst Rev. 2004

CRASH 2 Trial of Tranexamic Acid

- "A Large Randomized Placebo Controlled Trial Among Trauma Patients With, or at Risk of, Significant Hemorrhage, of the Effects of Antifibrinolytic Treatment on Death and Transfusion Requirement"
- Primary Outcome: Death within four weeks
- Secondary Outcome: transfusion, further surgery, venous thromboembolism

Goal: 20,000 patients under recruitment 2005-09

Reversal of Clopidigrel

- **Selectively inhibits ADP binding to platelet receptor and activation of GPIIb-IIIa complex**
- **Inhibits aggregation for platelet lifespan (7 days)**
- **No active metabolite, so no effect on new platelets after two hours**
- **Wears off in 5-7 days, or new platelets will work**
- **"Platelet transfusion may be used to reverse the pharmacological effects of clopidogrel when quick reversal is required."**

Bristol Myers Squibb package insert

Reversal of Platelet Inhibition

- **Renal failure, liver failure and NSAID use**
- **Three strategies:**
  - **Desmopressin (DDAVP)**
  - **Dialysis in renal failure**
  - **Platelet transfusion?**
- **Desmopressin**
  - **Not studied for ICH**
  - **Some effectiveness in renal failure patients**
  - **Increases Von Willibrand factor levels/activity**
  - **shortens bleeding time with aspirin and ticlopidine**
  - **In vitro, "may improve" platelet dysfunction caused by glycoprotein IIb/IIIa inhibitors or aspirin**

Mannucci PM, Vicente V, Blood, 1986
Churchill WH, Hematology, Transfusion Therapy,2000.

ASA: Platelet Transfusion?

- **Not studied for ICH**
- **RR of death at 3 months is 2.5 (CI 1.3-4.6) with ASA use**
- **Aspirin associated with hematoma growth in first week**
- **ASA half life only 20 minutes (metabolites 2 hours)**
- **Platelet transfusion theoretically beneficial**
- **"Whether the benefits of…platelet transfusion outweigh the risks in aspirin-associated ICH requires further study"**
- **"Transfusion is appropriate in a bleeding patient whose platelet count is adequate but whose platelets are nonfunctional as a result of medications such as aspirin NSAIDs or uremia"**

Saloheimo P, Ahonen M, Stroke, 2006
Churchill WH, Hematology, Transfusion Therapy,2000.

Case Study: Coumadin Anticoagulation

- **Vitamin K 10 mg IV**
- **FFP 6 units IV**
- **Prothrombin Complex Concentrate 50 units/kg = 3500 units IV**
- **No proven benefit to activated factor VIIa**

Case 2: NSAID Use

- **Desmopressin**
  - **0.3 mcg/kg = 2 mcg = 0.5 cc IV diluted in 100 cc over 15 minutes**
- **Platelet transfusion?**
  - **Unclear benefit**
  - **One unit raises platelet count 5-10K**
  - **Common to give 10 units in life threatening bleeds**

Should I Call or Transfer to a Neurosurgeon?

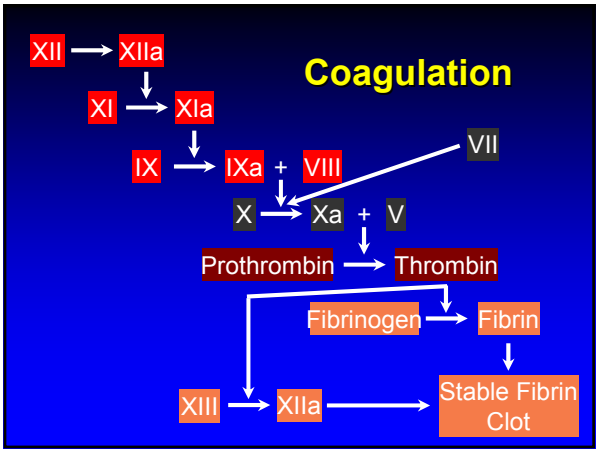
- Cerebellar ICH > 3 cm with deterioration, brainstem compression (coma) and/or hydrocephalus should….ASAP (Class I, Level B)
- Lobar clots within 1 cm of surface… "might be considered" (Class IIb, Level B)
- Routine evacuation of supratentorial ICH is not recommended

AHA/ASA Guidelines, *Circulation*, 2007

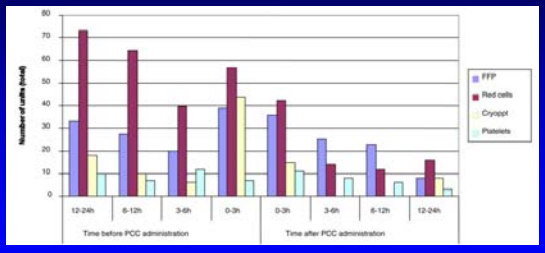
Conclusions

- Coagulopathy puts patients at high risk for ICH
- Vitamin K effective but too slow
- FFP effective but slow and volume overload
- Protamine works to reverse heparin
- Prothrombin Complex Concentrates promising
- Platelet transfusion might help for clopidogrel
- Factor VIIa unproven and expensive
- Tranexamic acid promising/under intense study

Questions?



Units of blood products administered: Before and after PCC administration



Bruce and Nokes, *Critical Care* 2008; 12:r105