Reversal of liver coagulopathy with recombinant factor VIIa before invasive procedures

S. Jean Chai MD & B. Gail Macik MD

University of Virginia Health Center

Department of Hematology/Oncology

Charlottesville, VA

Disclosure Statement: Dr. Macik is a member of the International Advisory Committee for Novo Nordisk, Inc for which she receives a consultant fee.

The coagulopathic patient

A 23 yo WF with a major depression is brought to the ER after an overdose of acetaminophen. She is diagnosed with fulminant hepatic failure and quickly deteriorates. Her mental status is poor and she is coagulopathic.

You are consulted to correct the patient's coagulopathy so that procedures can be performed, such as placement of an intracranial pressure monitor and central venous access, as well as a liver biopsy.

The coagulopathic patient - labs

Acetaminophen level 189

AST 9,360 ALT 10,770

Alk Phos 110

PT >120 INR >12

PTT 61.8 Fibrinogen 120

Agents used to correct coagulopathy

- FFP – all proteins present but not concentrated
- Cryoprecipitate – best source of fibrinogen/FXIII
- Vitamin K – effective in 24 hours IF liver works
- DDAVP – may help cirrhotic platelet dysfunction
- Estrogens – IF effective takes days/weeks
- Aminocaproic acid (Amicar) –helps if fibrinolysis evident
- Clotting factor concentrates – PCC have FII/VII/IX/X in higher concentration but may be thrombogenic

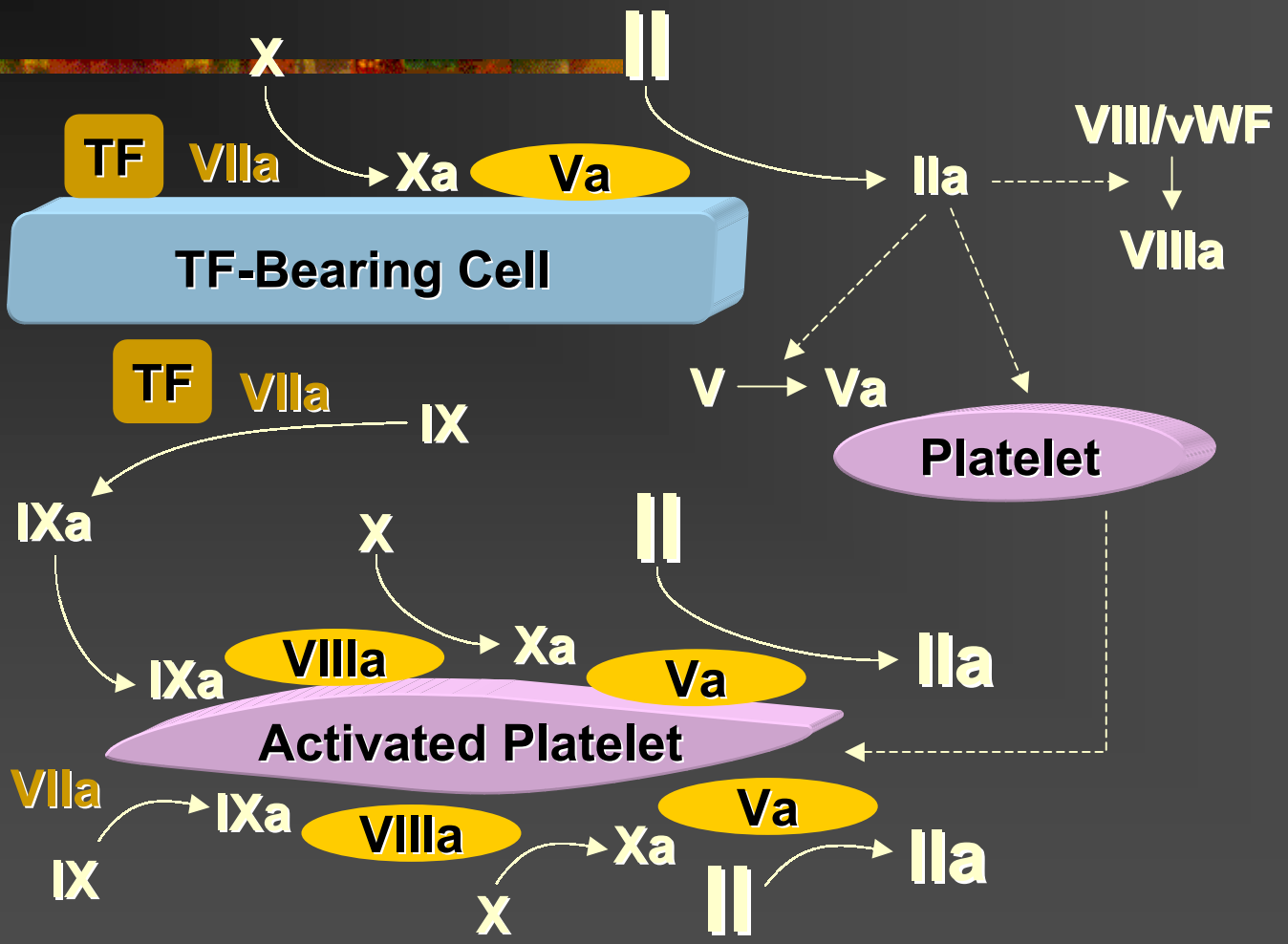
Fresh Frozen Plasma

- Contains 250 cc colloid
- In severe coagulopathy, start 20-30 cc/kg of FFP to correct the PT/INR. This translates to ~**6-10u FFP or 1.5-2.0 L of colloid**.
- Major problem, the half-life of VIIa is 4-6 hours; therefore, **frequent and large doses of FFP** are often needed.
- Other clotting factors have longer half-lives and can be adequately replaced by FFP and/or cryoprecipitate.

Complications of FFP

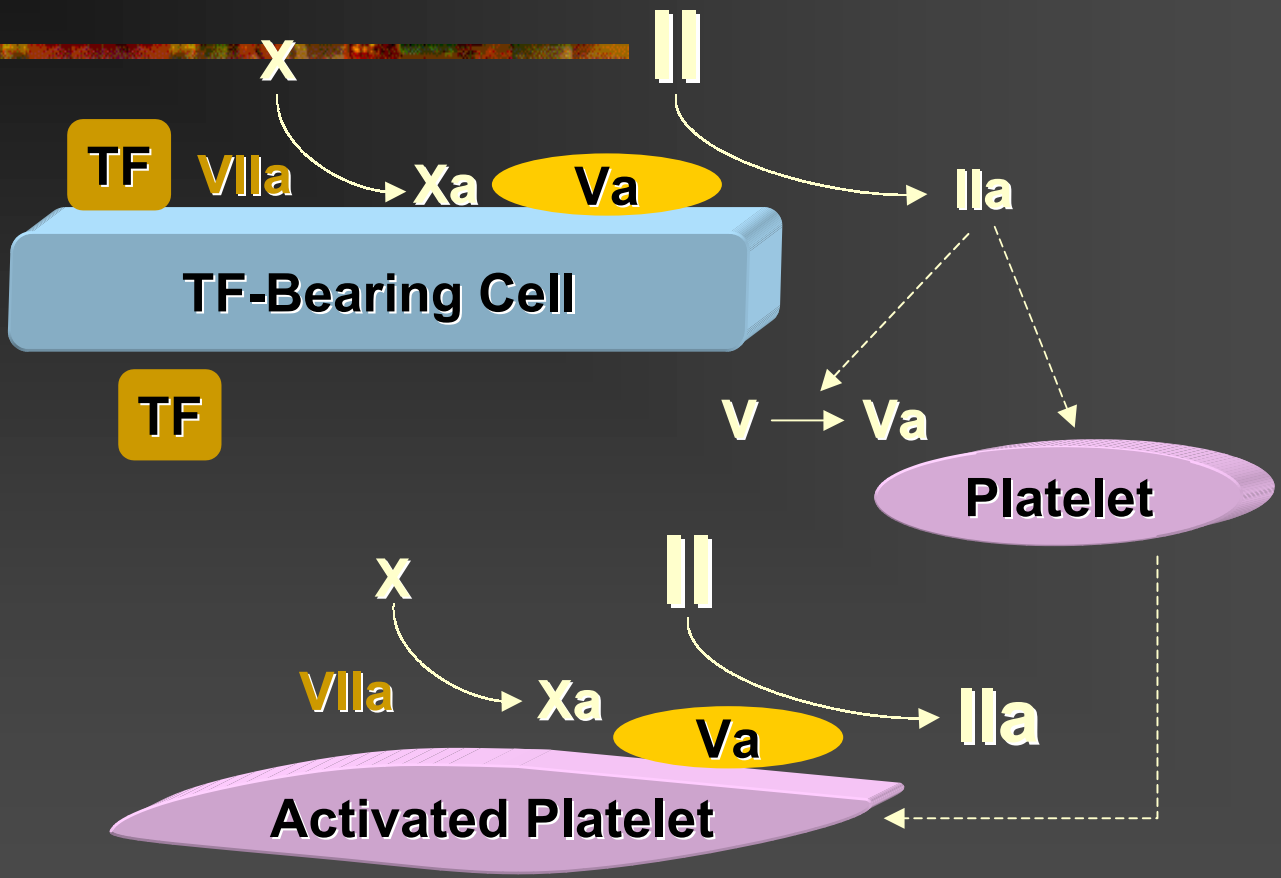
- In liver failure due to cirrhosis, fulminant hepatic failure, or sepsis, such large doses of colloid quickly lead to complications:
  - Volume overload - Anasarca
  - Pulmonary edema
  - Cerebral edema

Normal Hemostasis



Reproduced with permission from:
Hoffman M, et al. *Blood Coagul Fibrinolysis*. 1998;9(suppl 1):S61-S65.

FVIIa Mechanism of Action

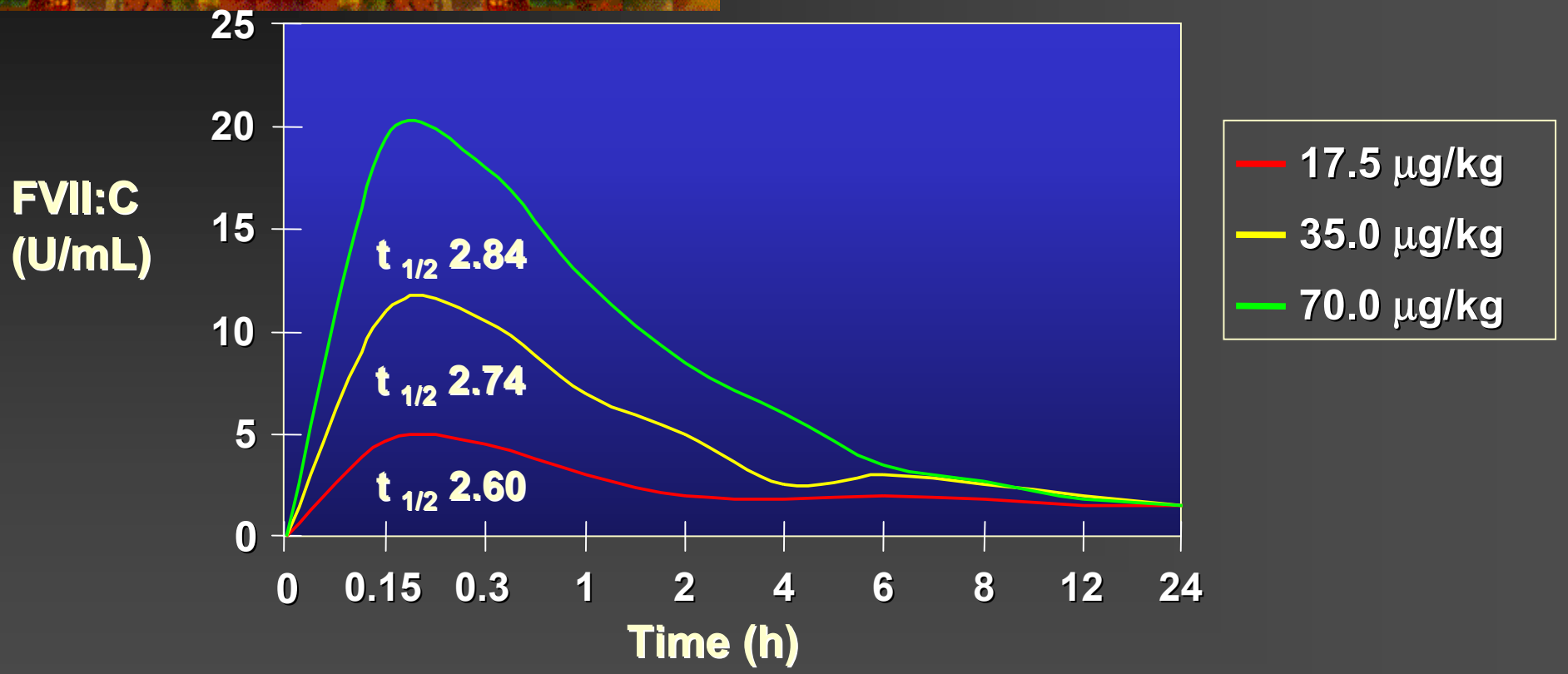


Reproduced with permission from:
Hoffman M, et al. *Blood Coagul Fibrinolysis*. 1998;9(suppl 1):S61-S65.

Rationale to use rFVIIa

- Correction of coagulopathy can be difficult especially in patients with liver dysfunction
- A variety of blood products and pharmacological agents are used for this purpose, but are often not efficacious due to side effects
- rFVIIa can be given IV push, volume 10-30cc over 1-2 minutes. This allows rapid correction of coagulopathy with minimal volume expansion.

Pharmacokinetics: Adults

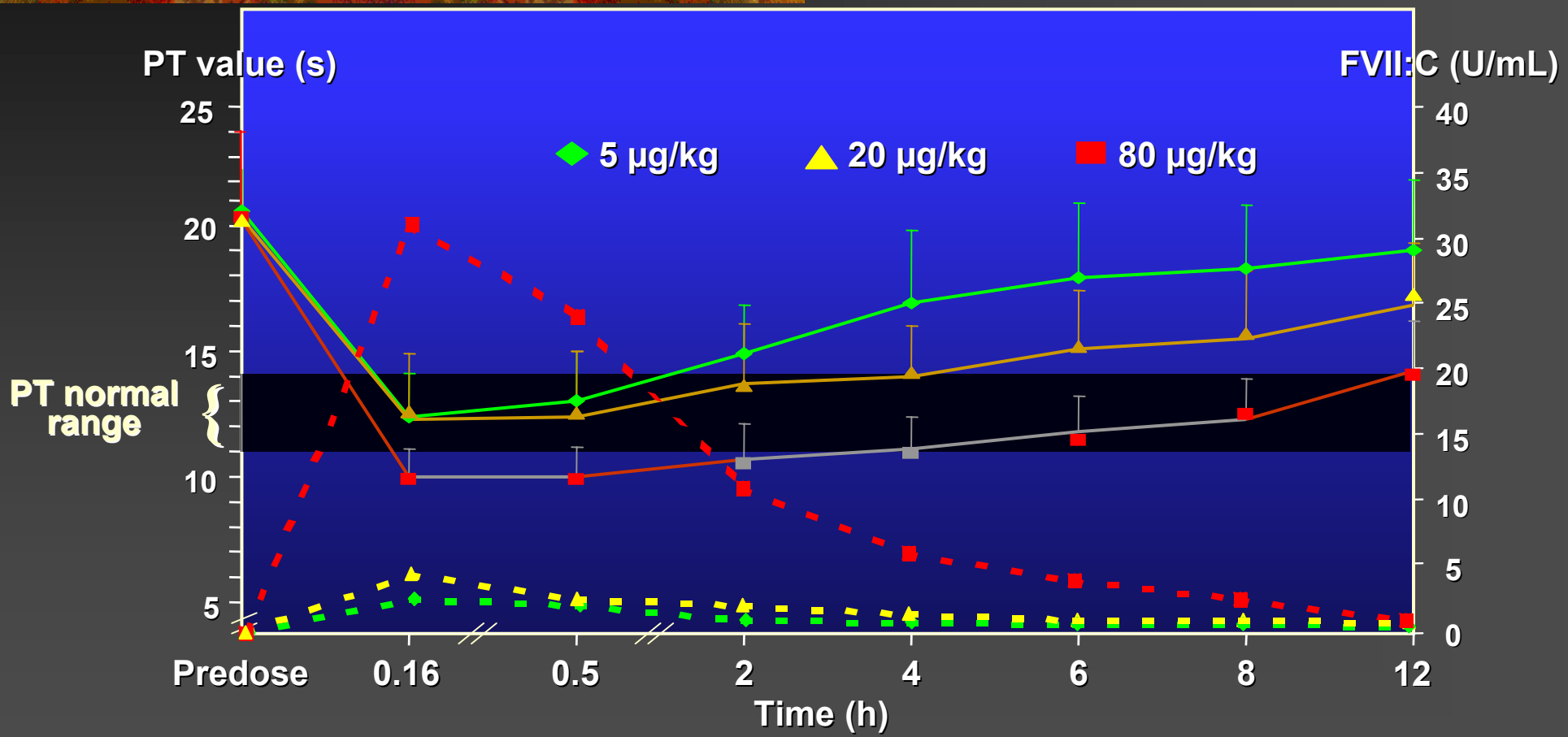


Mean $t_{1/2}$ of rFVIIa is independent of dose level

Reproduced with permission from:
Lindley CM, et al. *Clin Pharmacol Ther*. 1994;55:638-648.

Liver Disease

Effect of rFVIIa on PT Values and FVII Levels*†



*Mean values (SD). Normal range 11 to 14 s (shaded area).
†*P*<0.001 for all dose levels compared with baseline.
Bernstein DE, et al. *Gastroenterology*. 1997;113:1930-1937.

PT (s)
FVII:C levels

Further Studies

- Jeffers et al. performed a randomized, blinded, dose-escalation study with rFVIIa
- Doses given: 5, 20, 80 and 120 mcg/kg prior to laparoscopic liver biopsy
- 71 patients
- End points included pre- and post- PT, as well as direct visualization of hemostasis at the time of laparoscopy.
- One dose of rFVIIa was given 10 minutes prior to laparoscopy

Jeffers et al. "Safety and Efficacy of Recombinant Factor VIIa in Patients with Liver Disease Undergoing Laparoscopic Liver Biopsy." **Gastroenterology**. 2002;123:118-126.

Further Studies – Jeffers et al.

- No correlation between time to hemostasis and duration of correction of PT.
- High dose rFVIIa does not appear to be necessary.
  - 20, 80, & 120 mcg/kg doses corrected PT to a similar extent. 5 mcg/kg dose corrected PT to a lesser extent.
  - No difference in observed bleeding between any dose
  - 48 patients (74%) achieved hemostasis by 10 minutes after laparotomy.
  - 17 patients (26%) did not achieve hemostasis at >10 minutes and required a “rescue dose” of 80 mcg/kg rFVIIa.

Use of recombinant factor VIIa

- Retrospective chart review at UVA
- Between 3/4/00 and 1/15/01
- Activated recombinant factor VII (rVIIa) (Novo-seven) to reverse coagulopathy in 43 patients
- Coagulopathy not caused by a factor VIII or IX inhibitor

Use of rFVIIa at UVA

- Thirty-seven patients received **prophylactic** rFVIIa to reverse a coagulopathy in order to have a procedure or surgery.
  - The usual cause of the coagulopathy was cirrhosis or liver failure due to sepsis/shock
  - The vast majority had no complications during the planned procedure.
- Six patients received rFVIIa to **treat** bleeding

Dosing of rFVIIa

- In patients with a factor VIII inhibitor (FDA indicated use of rFVIIa)
  - Dose of 90-120 mcg/kg every 2 hours
- We used a number of different schedules
- Typical schedule was **40 mcg/kg** loading dose followed by 3-5 maintenance doses of **20 mcg/kg**

Prophylactic hemostatic agents

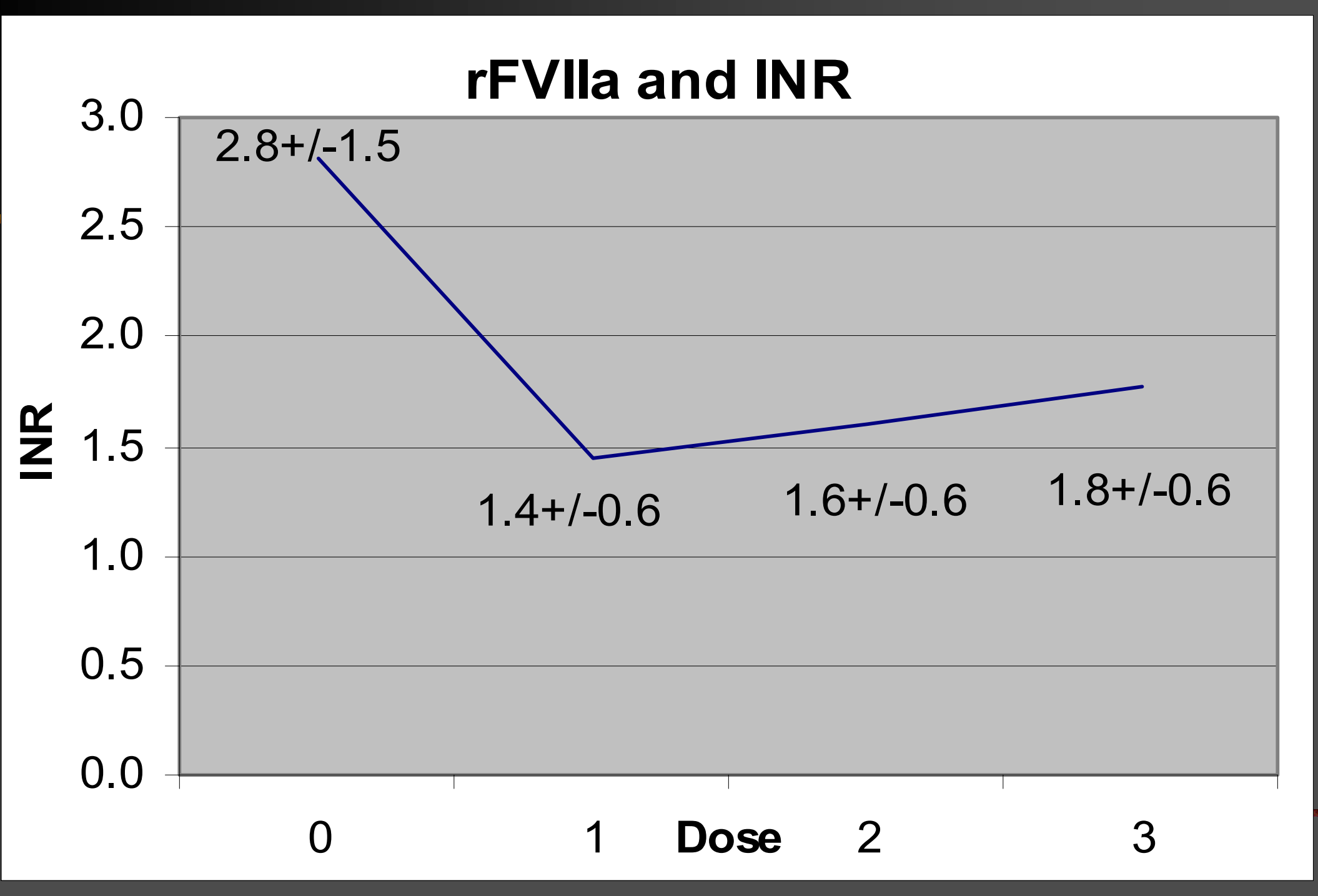
- Prior to giving rFVIIa, patients received
  - Vitamin K: 13.6 +/- 21.6mg
  - FFP: 4.1 +/-5.1U
  - Cryoprecipitate: 3.2 +/-5.6U
- Mean loading dose of rFVIIa was 45.5 +/- 17.5 mcg/kg
- Maintenance doses of 35.0 +/-18.6 mcg/kg
- 17 of 37 patients received one or two doses; the other patients received 3-13 doses

Reasons for use of rFVIIa

- Thirty-seven patients underwent 50 procedures
  - 33/37 liver dysfunction
  - 2/37 warfarin
  - 1/37 trauma
  - 1/37 sepsis

Procedures requiring use of rFVIIa

- 11 central line placements
- 8 liver biopsies
- 5 intra-cranial pressure monitor placements
- 4 TIPS procedures
- 3 epidural abscess drainages
- 3 upper endoscopies
- 3 arterial angiographies
- 2 liver transplants
- 2 cerebral AVM repairs
- 1 hepatic artery embolization
- 1 hemicraniotomy
- 1 paracentesis
- 1 drainage of a groin hematoma
- 1 ERCP
- 1 percutaneous trans-hepatic cholangiogram
- 1 PEG
- 1 femoral neck fracture fixation.


rFVIIa and INR
3.0
2.5
2.0
1.5
1.0
0.5
0.0
INR
2.8+/-1.5
1.4+/-0.6
1.6+/-0.6
1.8+/-0.6
0
1
Dose
2
3

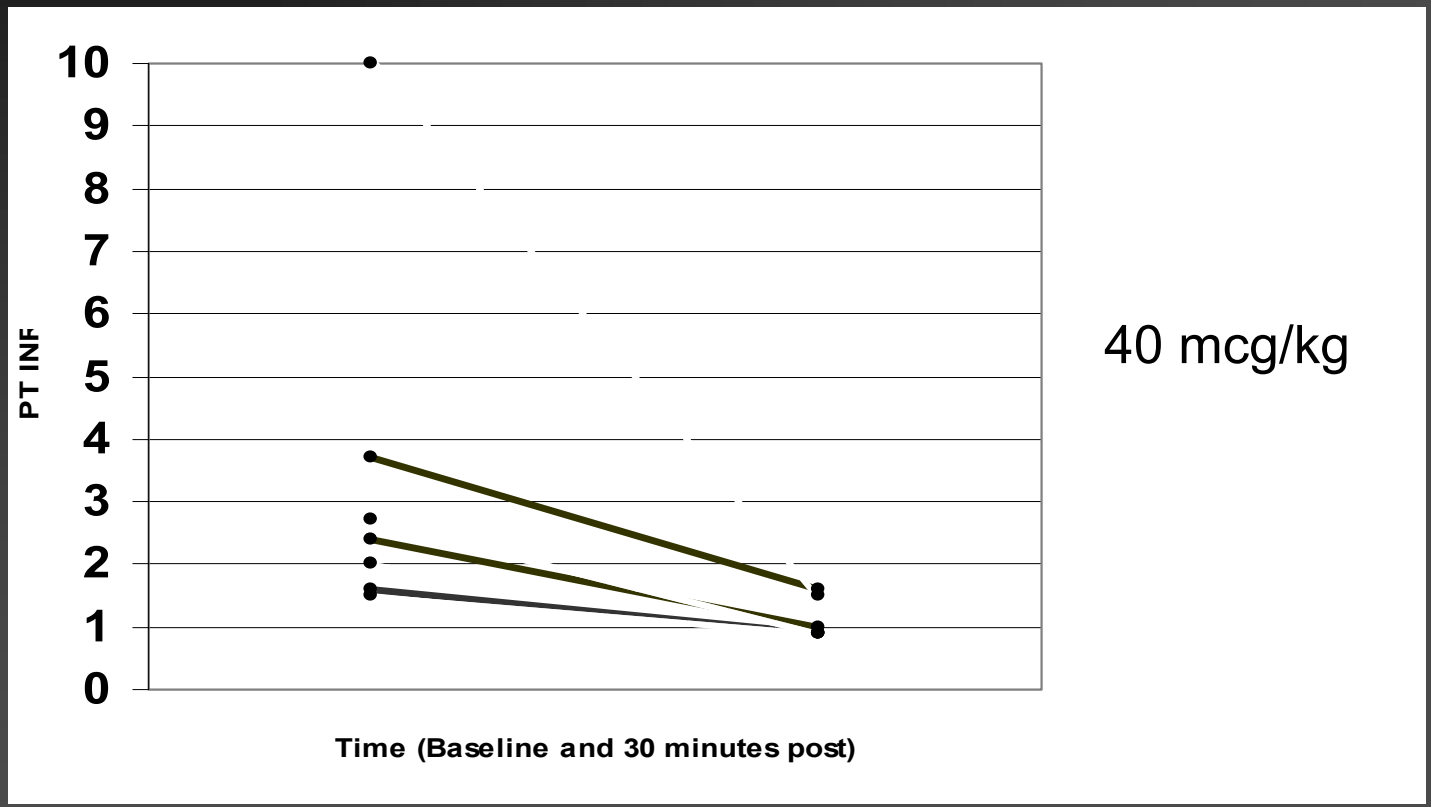
Fulminant Liver Failure Patients rFVIIa versus Historical Controls

	Control N=8	rFVIIa N=7	p-value
Tylenol-induced	(4/8) 50%	(4/7) 57%	1
PT-INR < 1.3	(0/8) 0%	(7/7) 100%	**0.0002**
ICP transducer	(3/8) 38%	(7/7) 100%	**0.03**
Ave units of FFP	19 (6-46)	13 (0-28)	0.35
Anasarca	(7/8) 88%	(2/7) 29%	**0.04**
Bleeding	(2/8) 25%	(0/7) 0%	0.47
Liver Transplant	(3/8) 38%	(3/7) 43%	1
Death*	(6/8) 75%	(1/7) 14%	**0.04**

* 5 of the 7 deaths were due to cerebral edema

Shami, VM Liver Transplantation . 9:138-143, 2003.

The PT INR Response a Subset of Patient with Fulminant Liver Failure



Results - Prophylactic rFVIIa

- The pharmacy cost for the rFVIIa ranged from $3,008.57 to $43,085.25 with a mean cost of **$12,746.64** +/-$10,228.50.
- In the 24-hour period after receiving rFVIIa, these patients received a mean of 1.2 +/- 1.9U red blood cell transfusions.

Complications with prophylaxis

- Only four patients had complications
  - ST-elevation myocardial infarction, but had recent cocaine use and was on norepinephrine. Subsequent cardiac catheterization showed no evidence of coronary artery thrombus.
  - Inability to remove an arterial sheath post-angiogram due to INR > 1.8 at the end of the procedure. The sheath was later removed.
  - Continued bleeding during an EGD-bleeding started during the procedure and more FVIIa was not given
  - Atrial fibrillation after a dose of rFVIIa

Prophylaxis with rFVIIa - Discussion

- Recombinant factor VIIa appears safe to use in patients with coagulopathy not due to factor VIII inhibitor.
- rFVIIa appears effective in correcting coagulopathy due liver dysfunction, but requires a fibrinogen > 120 mg/dl.
- The cost-effectiveness of this approach is unknown.
- Further studies are required before such use can be considered standard of care.

UVA Current Practice - rFVIIa

- Available to patients with coagulopathy due to hepatic dysfunction or warfarin in order to rapidly correct PT/INR prior to a procedure, especially when volume overload is an issue (ARF, hepatorenal syndrome, intra-cranial hemorrhage etc.)
- Requires approval by Hematology Consult on a case by case basis.
- Available to patients with proven inhibitor of factor VIII or IX.

UVA Current Practice - rFVIIa

- Ensure fibrinogen >120 with cryoprecipitate
- 40 mcg/kg IV initial dose
- Patient taken for procedure within 1 hour
- 20 mcg/kg IV maintenance dose at 2hrs and 4 hrs to prevent peri-operative hemorrhage

Areas of future investigation

- Prophylactic use of rFVIIa in coagulopathy due to hepatic dysfunction: blinded, prospective dose-escalation study
- Use of rFVIIa as a “universal” pro-coagulant for trauma, surgical bleeding, uremic bleeding and DIC: case reports only.
- Use of rFVIIa for platelet dysfunction like Glanzmann’s thrombasthenia and von Willebrand’s disease – case reports only.