Clinical use of prothrombin complex concentrate

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Content of the presentation

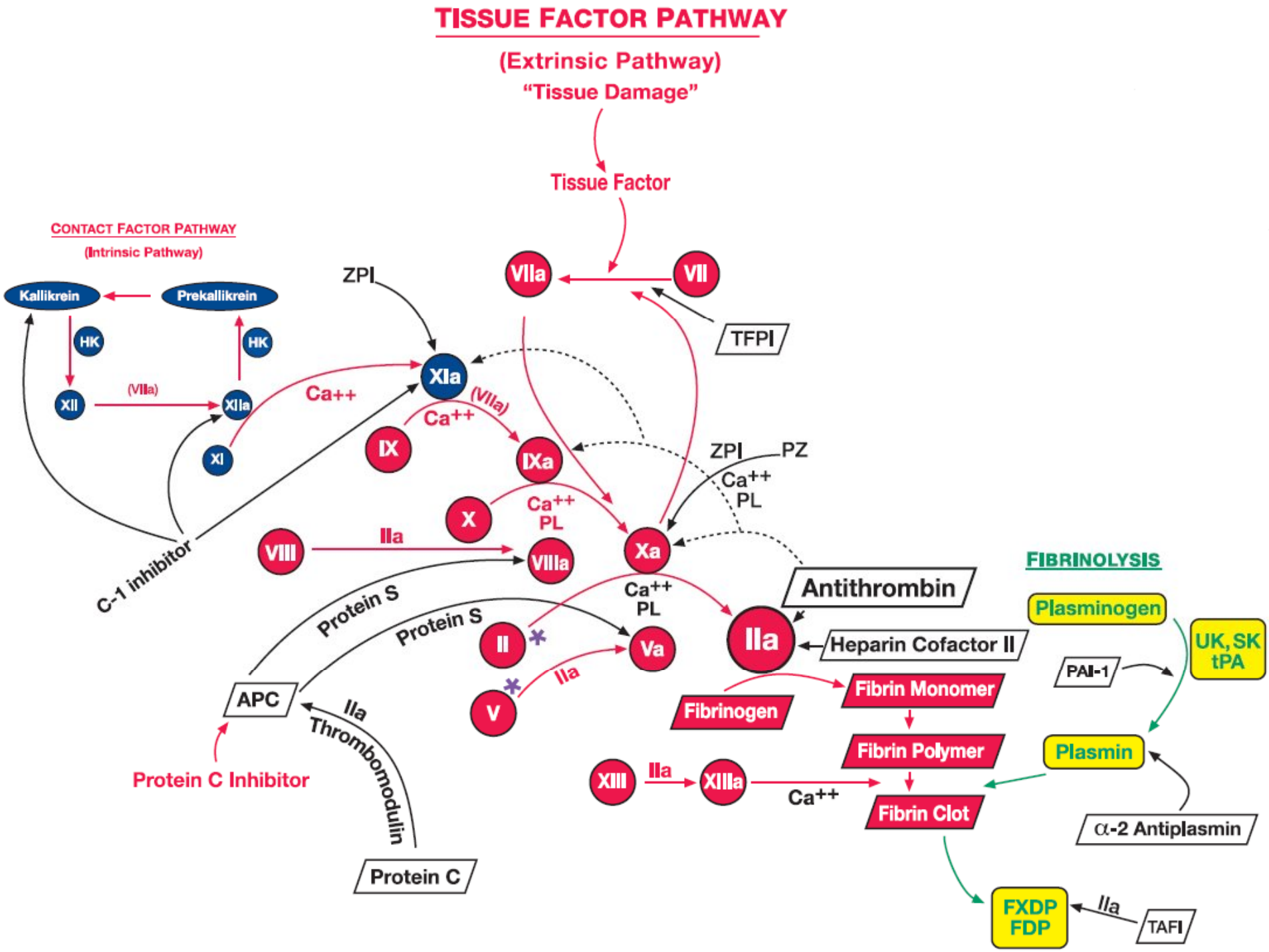
Prothrombin complex concentrates

- Liver disease as an example of medical condition
- Warfarin and vitamin K
- Critical illness and bleeding tendency
- Coagulopathy in trauma
- Warfarin reversal
- Optimal use of PCCs
- Comparison with FFP

Take home messages

Prothrombin complex concentrates

- All are not the same
- Are highly effective in several clinical applications
  - surgical and other invasive interventions
  - trauma
  - serious bleeding
  - warfarin reversal
- Modern PCC can be used without any apparent risk for the patients


TISSUE FACTOR PATHWAY
(Extrinsic Pathway)
"Tissue Damage"
Tissue Factor
CONTACT FACTOR PATHWAY
(Intrinsic Pathway)
Kallikrein
Prekallikrein
HK
HK
XII
(VIIa)
XIIa
XI
Ca++
ZPI
VIIa
VII
TFPI
XIa
(VIIa)
Ca++
IX
IXa
ZPI
PZ
Ca++
PL
X
Ca++
PL
VIII
IIa
VIIIa
Xa
C-1 inhibitor
Protein S
Protein S
Ca++
PL
Antithrombin
IIa
Heparin Cofactor II
II
Va
APC
IIa
Thrombomodulin
V
IIa
Fibrinogen
Fibrin Monomer
Fibrin Polymer
Protein C Inhibitor
XIII
IIa
XIIIa
Ca++
Fibrin Clot
Protein C
FIBRINOLYSIS
Plasminogen
UK, SK
tPA
PAI-1
Plasmin
α-2 Antiplasmin
FXDP
FDP
IIa
TAFI

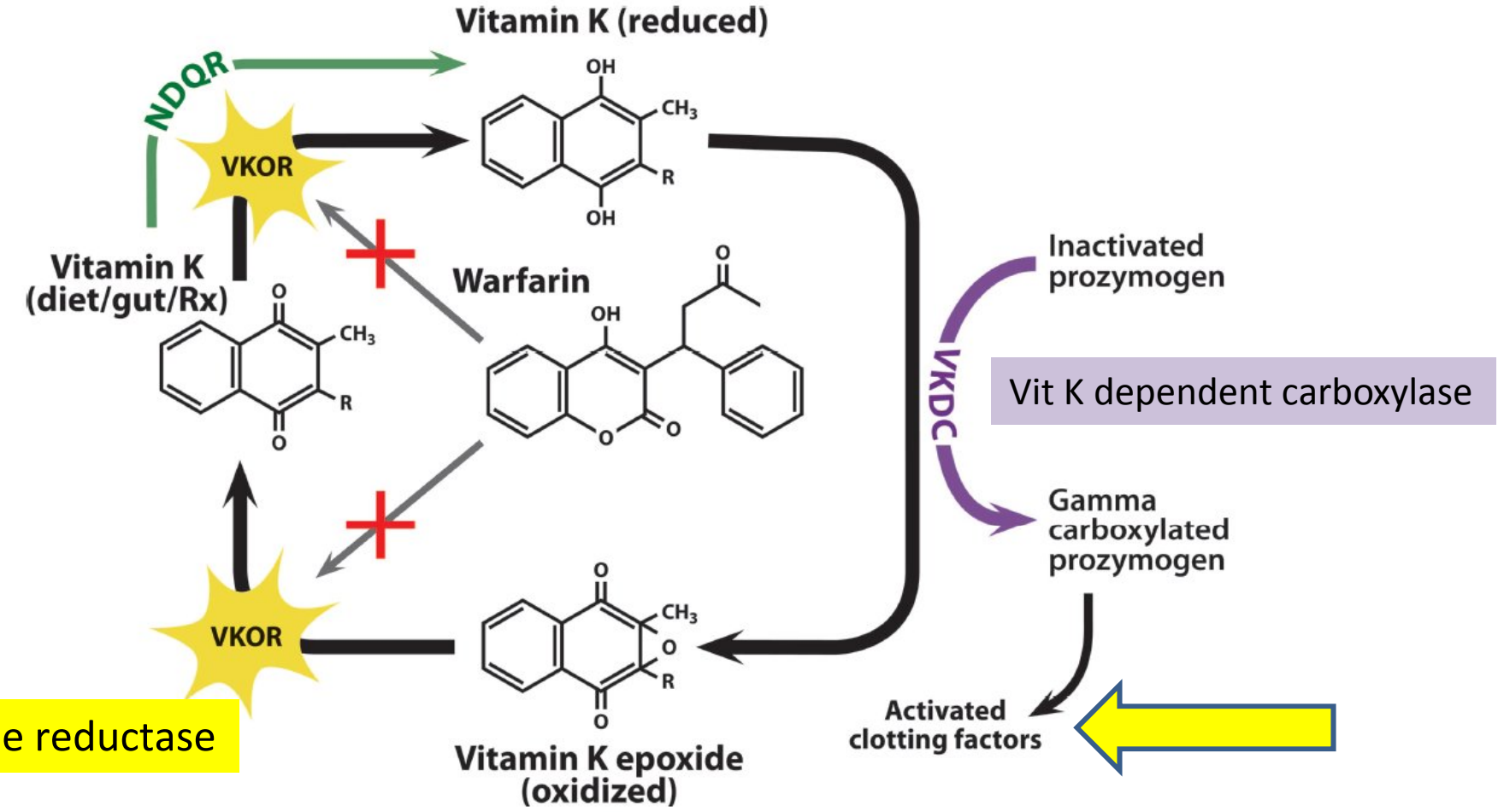
Vitamin K-dependent clotting factors

- Coagulation factors II, VII, IX, X
- Natural anticoagulants: protein S, C and Z

Deficiency:

1. Very rare genetic or inborn errors of the blood clotting system
2. Usually an acquired condition
    - Liver disease
    - Malabsorption
    - Coumarins overdose

Vitamin K antagonists



Koutrouvelis A, et al. Anesthesiology 2010:113:1192-7

Medical conditions

- Liver is the place of synthesis of
  - Most of clotting factors
  - Coagulation inhibitors
  - Fibrinolytic proteins
- Malabsorption of vitamin K
  - Disease of the biliary tract
  - Inflammatory bowel disease

Liver insufficiency

- A high risk for both spontaneous and procedure associated bleeding
  - Reduced levels of the vitamin K dependent coagulation factors
  - Low platelet count
  - Disturbed fibrinolysis

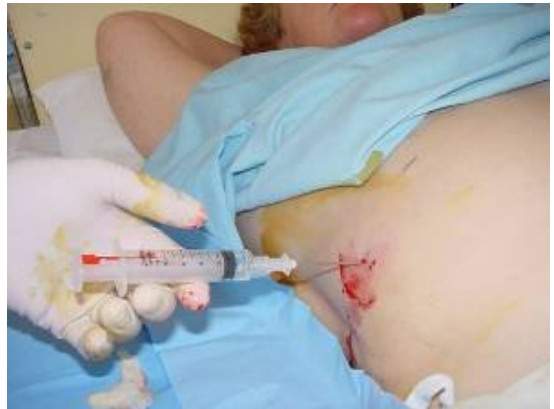
Major bleeding

Major blood loss is a life-threatening condition

- Definition of major bleeding?
- Most commonly in major surgery, trauma patients, deliveries
- Even after "minor" invasive diagnostic interventions

Common problems following liver biopsy

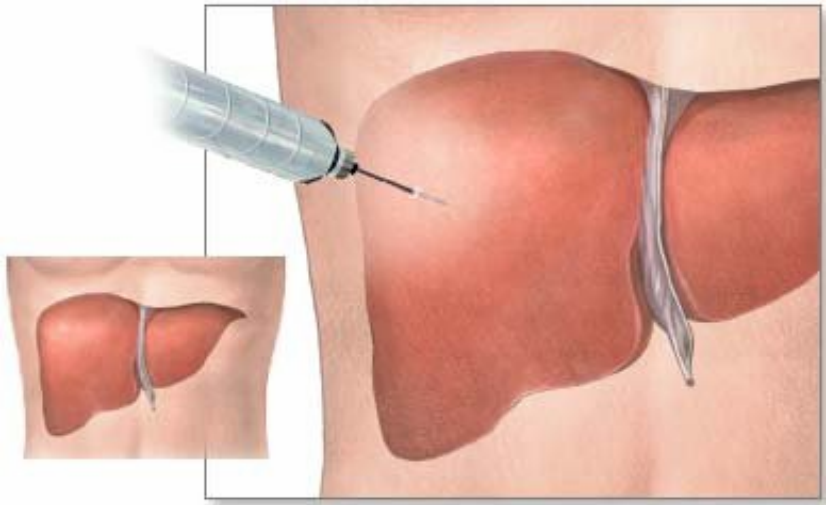
- Intraperitoneal hemorrhage
  - The main cause of mortality
  - 6 patients of 68000 percutaneous liver biopsies died from intraperitoneal hemorrhage (Piccininoet al. 1986)
- Significant hemorrhage (a drop in hemoglobin of >2g/dL)
  - 0.35% - 0.5% of all procedures (Knauer 1978, McGill et al. 1990)
- Subclinical bleeding
  - Up to 23% of patients intrahepatic or subcapsular haematomas detectable by ultrasound (Minuk et al. 1987)



Common problems following liver biopsy

- The INR should be checked before the biopsy

- Vitamin K
  - At least 12 hours prior to the biopsy
  - Most effective: biliary obstruction or malabsorbtion



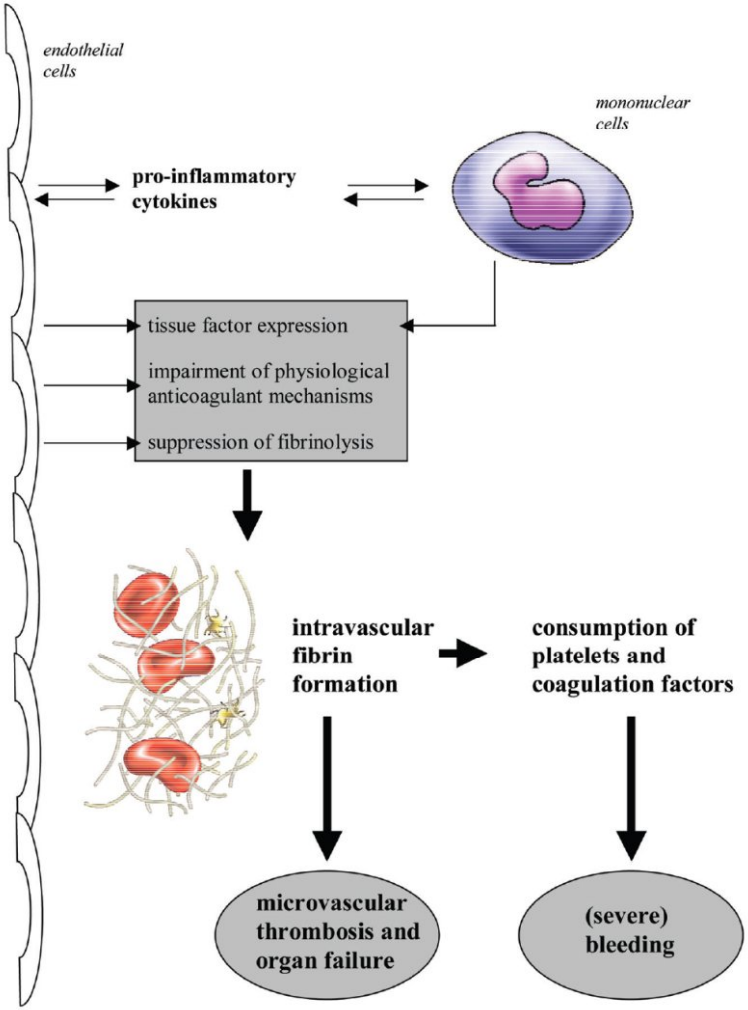
Common problems following liver biopsy

- If vitamin K is ineffective, then fresh frozen plasma
  - Spectoret al. 1966, Contreras et al. 1992
- FFP corrects the prothrombin time and increases critical coagulation factors to 0.3 IU/mL in only 20% of cases
  - Gazzard et al. 1975, Chowdhury P et al. 2004.

- FFP has only a limited place in prophylaxis prior to liver biopsy
  - British Committee for Standards in Haematology, Blood Transfusion Task Force. Br J Haematol. 2004.

Critical illness and bleeding tendency

- Common problem in ICU
  - Thrombocytopenia 35-45%
  - Prolonged PT and aPTT 30%
  - Elevated fibrin split products 40-99%
  - Low levels of coagulation inhibitors 40-90%



Levi M, Opal SM. Critical Care 2006

Critical illness and bleeding tendency

Treatment of underlying cause

- PCC may be used if global replenishment of coagulation factors is needed and volume load of FFP is not tolerated

Levi M, Opal SM. Critical Care 2006

Characteristics, management and outcomes of adults with major trauma taking pre-injury warfarin in a Western Australian population from 2000 to 2005: a population-based cohort study

- Warfarin reversal started 17 hours after injury
- The period between injury and completion of reversal was 54 hours

Mountain et al. MJA 2010; 193 (4): 202-206

Coagulopathy in trauma patients

- Counterintuitive, blood components, packed red blood cells (RBCs), plasma, or platelet concentrates, can cause hemodilution

- When a 500-mL blood donation is processed into leukoreduced components, 180 mL of additional solutions are added and 15 mL of the RBCs and half of the platelets are lost

Coagulopathy in trauma patients

- When the resulting 680 mL of components are transfused as a unit of RBCs, a unit of plasma, and a unit of platelets
  - hematocrit < 30%
  - coagulation factors ~ 60%
  - platelets 80 × 10^9/L (2/3 platelets will be viable)
  - fibrinogen 950 mg/L

Coagulopathy in trauma

- Retrospective analysis of German and Austrian databanks
- Major trauma patients with major bleeding and coagulopathy
  - German: FFP
  - Austrian: Fibrinogen and PCC

Nienaber U et al. Injury 2011

Nienaber U et al. Injury 2011

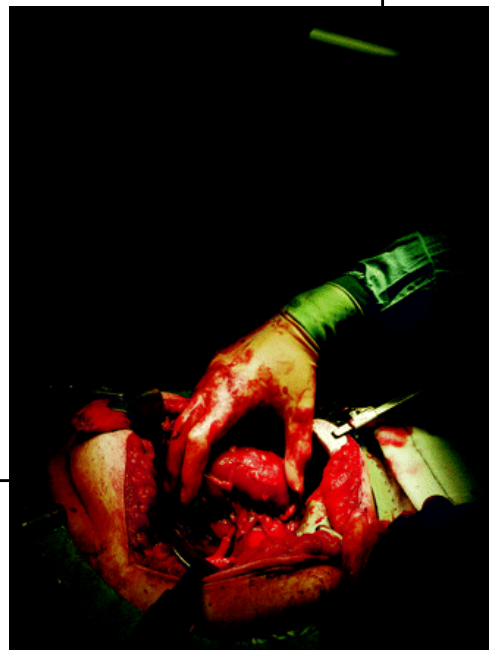
	FFP N=18	Fibrinogen and PCC N=18
Sepsis (n, %)	6 (33)	3 (17)
Multiple organ failure (n, %)	11 (61)	3(17) *
Ventilator days (days, range)	15 (6-22)	10 (5-20)
ICU LOS (days, range)	(13-25)	19 (9-33)
In hospital LOS	38 (21-48)	26 (19-50
In hospital mortality (n, %)	2 (11)	3 (17)

* p=0.015

Prothrombin complex concentrates

PCCs useful

- For the treatment of serious or life-threatening bleeding: perioperative or trauma
- Management and prevention of bleeding
  - Patients with liver disease
  - Patients on vitamin K antagonists



Warfarin reversal

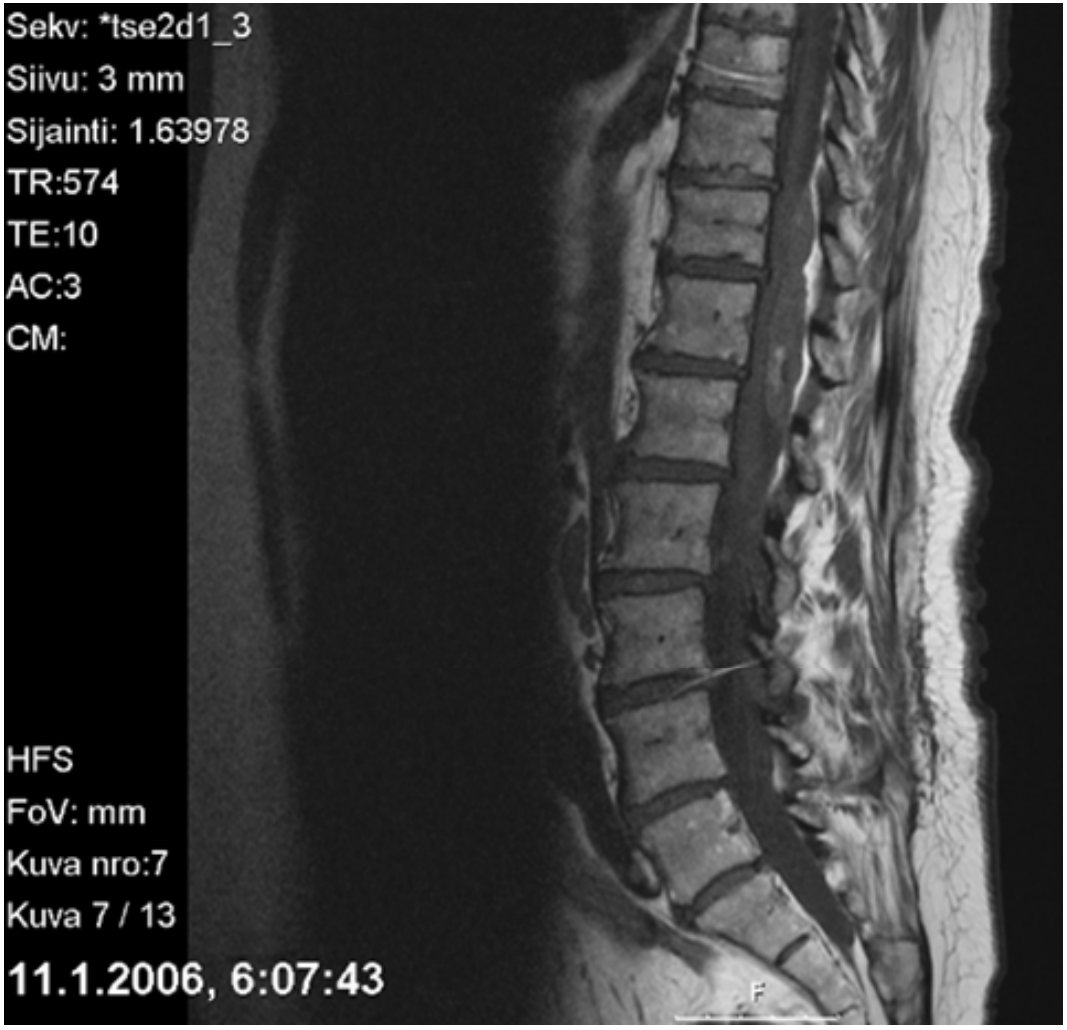
- Vitamin K po/i.v: slow
- PCC: fast, highly effective
- FFP: time consuming infusion, volume load, effective only on ~ 20%
- Factor VIIa: expensive

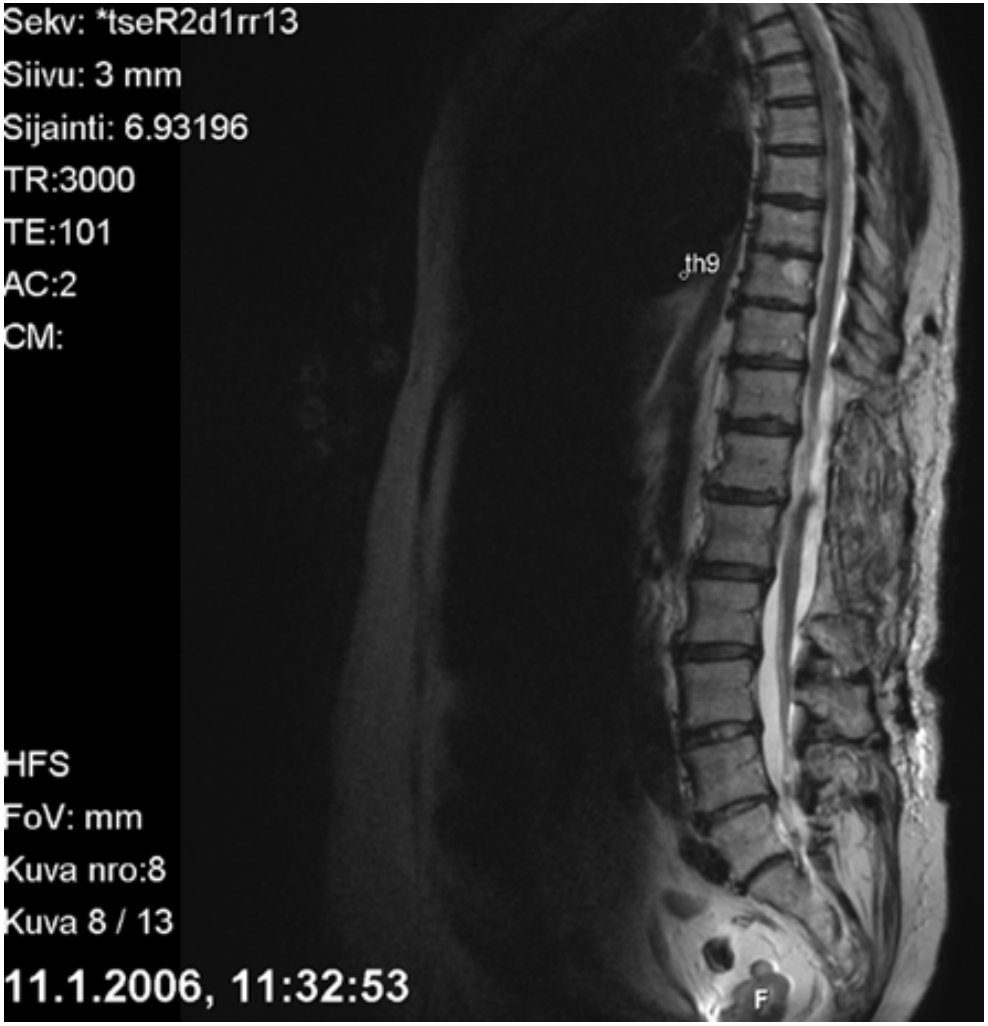
Warfarin reversal before central neuraxial blocks

In Kuopio one of the most common indication for PCC

- 'Bloody tap' is relatively common (3-4%) but it usually produces a clinically insignificant collection of blood in the epidural space

Epidural hematoma and myelopathy





Prothrombin complex concentrates

PCC:

- A sterile, freeze-dried combination of clotting factors II, VII, IX, and X
- And modern contain also protein C and protein S
- Some preparations contain also heparin

Prothrombin complex concentrates

- Some PCC low concentrations of factor VII (10-25 IU/ml)
  → Should be supplementated with FFP
- Some high concentration of prothrombin (factor II)
  → Increased risk for thrombotic complications

Composition of PCCs in the World Federation of Hemophilia Register of clotting factor concentrates

		International units relative to factor IX					
Brand name	Manufacturer	Factor II	Factor VII	Factor IX	Factor X	Viral inactivation	Additional information
Bebulin VH	Baxter BioScience, Austria	120	(13)	100	100	Vapour heat, 60°C for 10 hours at 190 mbar, then 80°C for 1 hour at 375 mbar	Heparin added
Beriplex P/N	CSL Behring, Germany	128	68	100	152	Pasteurisation at 60°C for 10 hours, and nanofiltration	Protein C; antithrombin, heparin and albumin added
Cofact	Sanquin, the Netherlands	56-140	28-80	100	56-140	Solvent/detergent and 15 nm nanofiltration	Antithrombin added
KASKADIL	LFB, France	148	40	100	160	Solvent/detergent	Heparin added
Octaplex	Octapharma, Austria and France	44-152	36-96	100	50	Solvent/detergent and nanofiltration	Heparin added; low activated factor VII content
Profilnine SD	Grifols, USA	148	(11)	100	64	Solvent/detergent	–
Prothrombinex VF	CSL Bioplasma, Australia	100	(–)	100	100	Dry heat, 80°C for 72 hours and nanofiltration	–
Prothromplex T	Baxter BioScience, Austria	100	85	100	100	Vapour heat, 60°C for 10 hours at 190 mbar, then 80°C for 1 hour at 375 mbar	Antithrombin and heparin added
UMAN Complex D.I.	Kedrion, Italy	100	(–)	100	80	Solvent/detergent and dry heat, 100°C for 30 minutes	Antithrombin and heparin added

Sorensen et al. Crit Care 2011:15:201-10

Prothrombin complex concentrates

Cofact® (concentrate of 4 coagulation factors)

• Factor II	14 – 35 IU/ml
• Factor VII	7 – 20 IU/ml
• Factor IX	25 IU/ml
• Factor X	14 – 35 IU/ml
• Protein C	12-26 IU/ml
• Protein S	3-5 IU/ml

Dosing of PCC

- Dosing is based on the factor IX content
  - After reconstitution 25 IU/ml
- Both fixed and weight-based dosing recommendations are available

- 70 kg patient
  - According SPC: weight-based 40 – 90 ml
  - In Kuopio: fixed doses 20 – 40 – 60 ml

Weight-based dosing of PCC

- In theory
  - 1 IU/kg should raise the plasma activity by 0.02 IU/mL
- Empirical finding
  - factor II 0.02 IU/mL
  - factor VII 0.01 IU/mL
  - factor IX 0.01 IU/mL
  - factor X 0.017 IU/mL

Fixed dosing recommendations of PCC

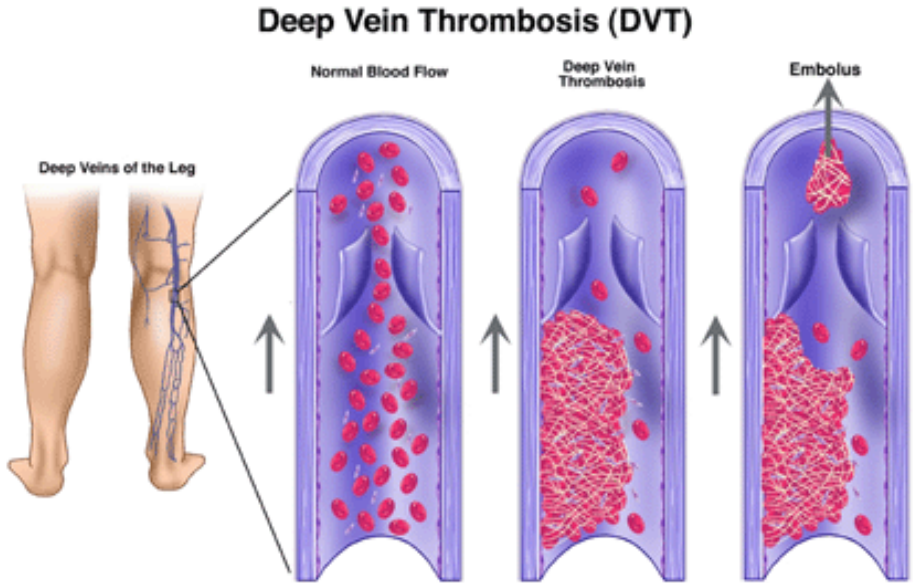
- 70 kg patient has 3000 ml of plasma
- 1 IU of a coagulation factor activity is equivalent to the quantity in one ml of normal human plasma
- Thus, 70 kg patient has 3000 IU of each coagulation factor

Fixed dosing recommendations of PCC

- 30% of the human coagulation factors is sufficient for clot formation
  - 900 IU is needed
- Factor IX 25 IU/ml:
  - 20 ml = 500 IU
  - 60 ml = 1500 IU — should be sufficient!
- FVII 10-20 IU/ml
  - 20 ml = 200 - 400 IU
  - 60 ml = 600- 800 IU — could be too little?

Prothrombin complex concentrates

- Avoid higher doses
  - PCC has been associated with thrombo-embolic complications and disseminated intravascular coagulation
  - Modern PCC seem to be safer

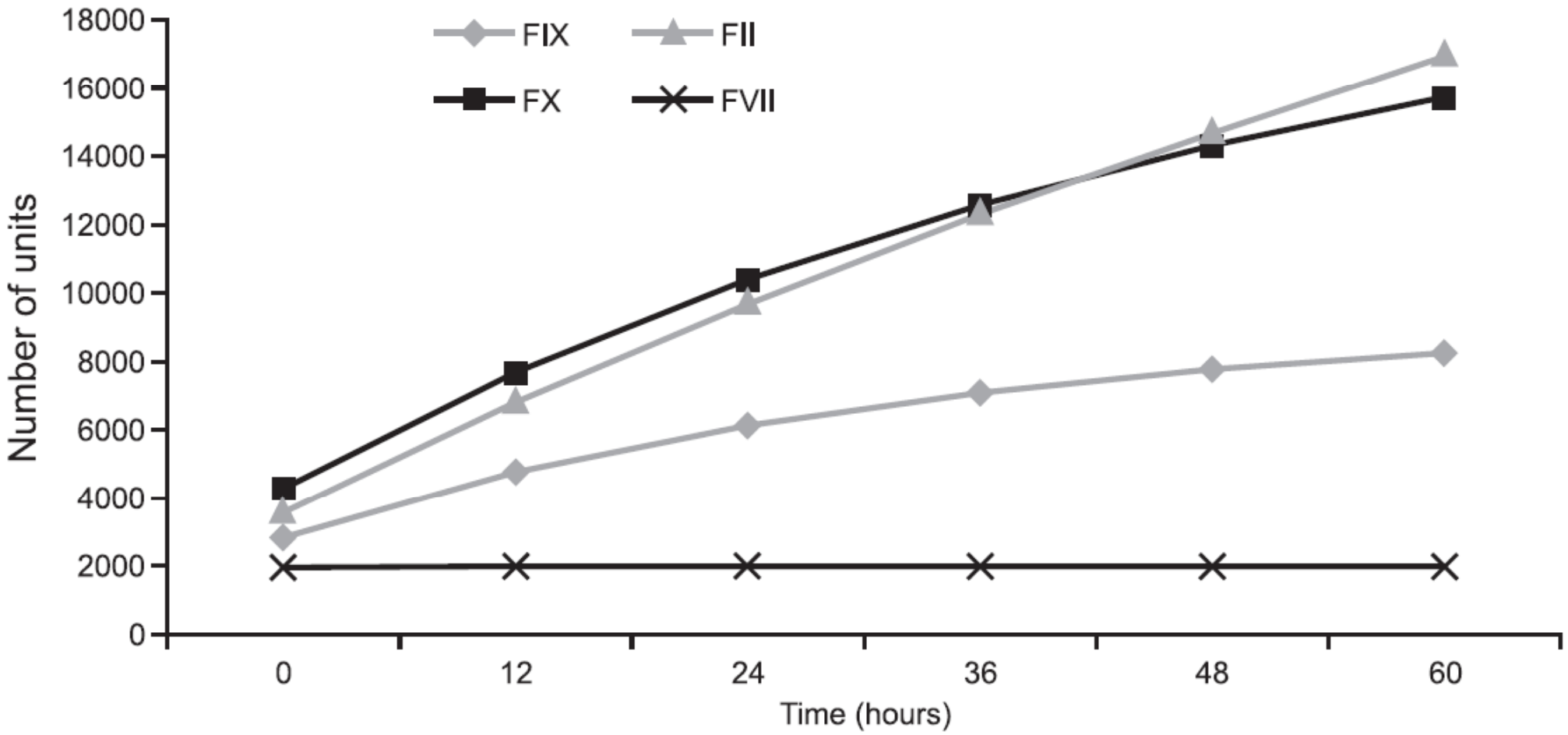


Sorensen et al. Crit Care 2011:15:201-10

Prothrombin complex concentrates

Coagulation factor	Half-life
• Factor II	40 - 60 hours
• Factor VII	4 - 6 hours
• Factor IX	18 - 25 hours
• Factor X	30 - 60 hours

PCC, adverse effects



Sorensen et al. Crit Care 2011:15:201-10

Prothrombin complex concentrates

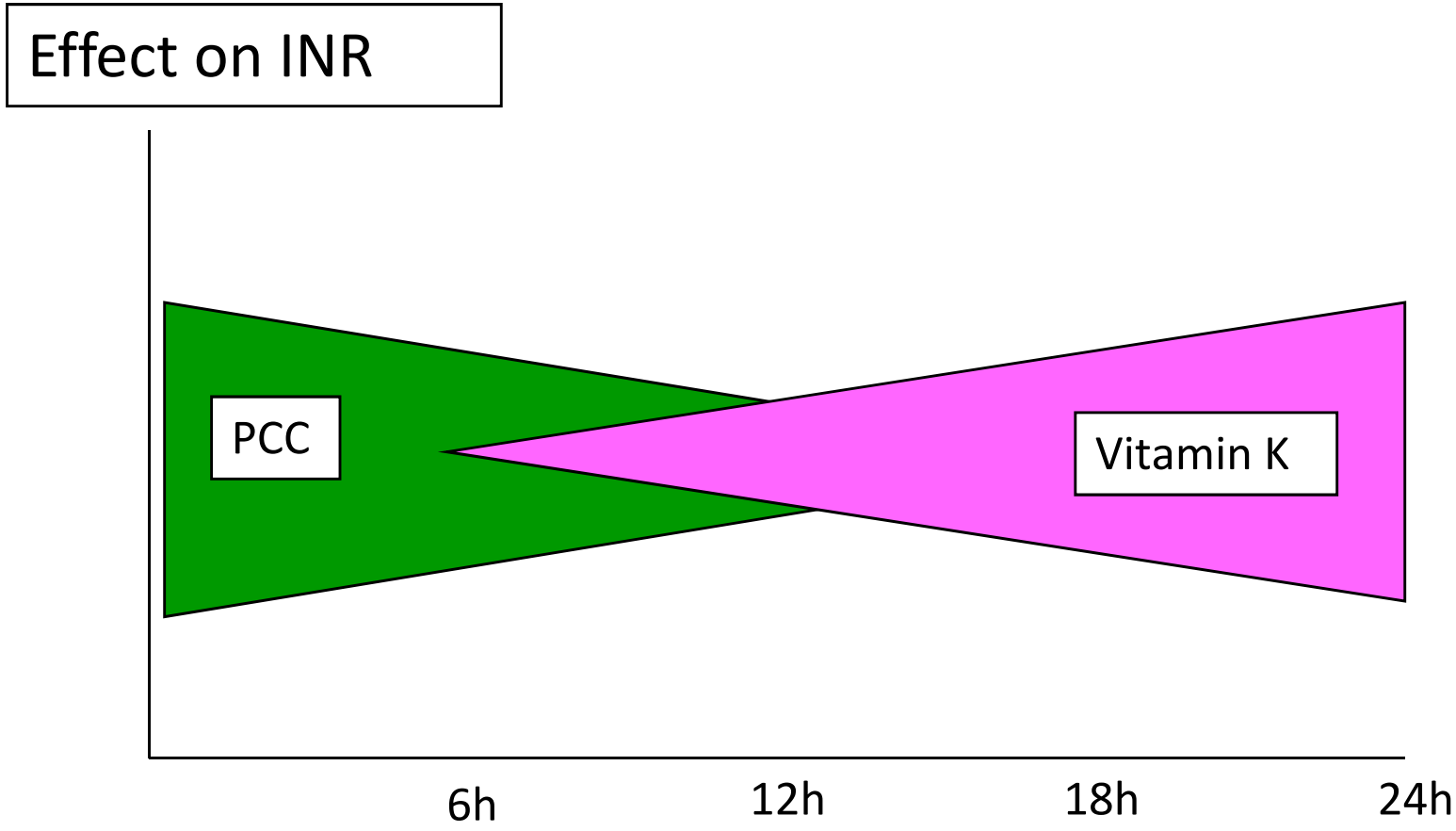
Therapeutic indications

- ✓ Treatment of bleeding
- ✓ Perioperative prophylaxis of bleeding
  1. In acquired deficiency of the prothrombin complex coagulation factors
  2. In congenital deficiency of any of the vitamin K dependent coagulation factors

Prothrombin complex concentrates

- The correction of impaired haemostasis persists 6-8 hours
  - $t\frac{1}{2}$ for FVII 4 - 6 h
- If vitamin K is administered simultaneously, repeated treatment with PCC may not be required
  - Vitamin K onset 6 h, full efficacy 24h

PCC and vitamin K



Fresh frozen plasma

FFP

- Fluid portion of human blood that has been centrifuged, separated, and frozen.
- Contains all coagulation factors, fibrinolytic and complement components, and some other proteins
- Adverse effects include allergy and fluid overload
- A potential for transmission of infections and transfusion reactions

Fresh frozen plasma

FFP

- The infusion time of FFP is relatively long
- Larger amounts of FFP are associated with
  - Risk of volume overload (TACO), that is risk in patients with cardiac insufficiency
  - Further hemodilution, which in turn may impair coagulation
- At any dose
  - Transfusion-related acute lung injury (TRALI)

Critical levels of coagulation factors

- Critical coagulation factor level of 20-30% of normal is needed for maintenance of hemostasis in patients undergoing invasive procedures
    - **In life-threatening bleeding 100%!**

Fresh frozen plasma

800 ml FFP

- Median changes
  - Factor II 0.03 → 0.17 IU/ml
  - Factor VII 0.05 → 0.19 IU/ml
  - Factor IX 0.1 → 0.19 IU/ml
  - Factor X 0.06 → 0.2 IU/ml

- Makris M et al. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. Thrombosis and Haemostasis 1997; 77:477-480.

Fresh frozen plasma- efficacy

- Most clinical uses of FFP recommended by guidelines are not supported by evidence of randomised trials

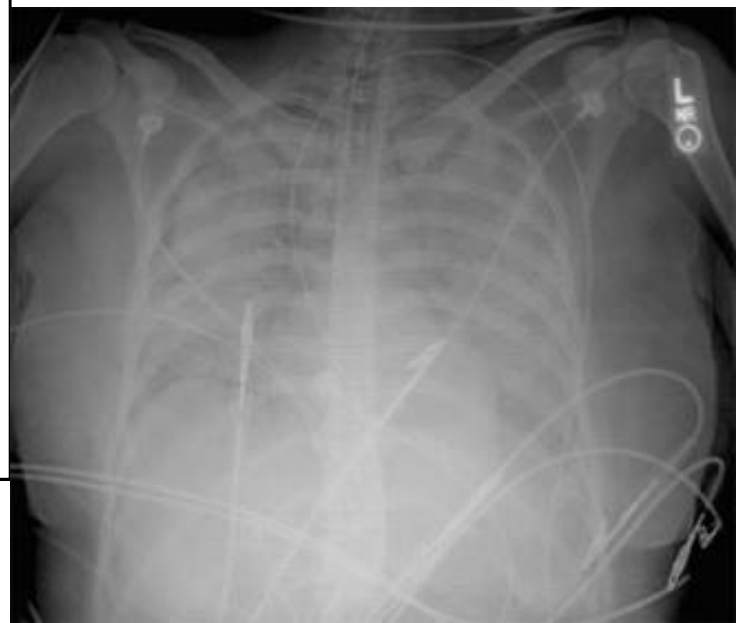
- Little evidence that FFP is an effective treatment

Stanworth SJ et al. Br J of Haematology 2004: 126:139-52

TRALI: Transfusion-related acute lung injury

- TRALI is particularly likely to occur with those with a large volume of FFP
- Noncardiogenic pulmonary edema resulting from immune reactivity of leukocyte antibodies
- Signs and symptoms will appear 1–2 h
- Hypoxia, fever, dyspnea, and even fluid in the endotracheal tube may occur
- Most patients recover in 96 h

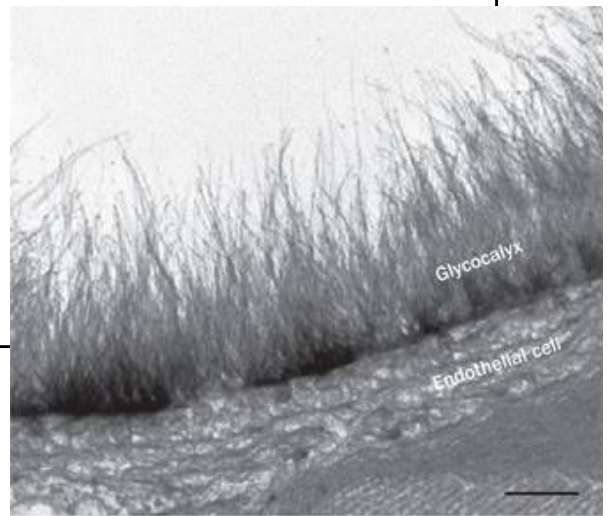
- TRALI is one of the most common causes of transfusion related deaths



Transfusion-associated circulatory overload (TACO)

Patients at risk for TACO

- Reduced left ventricular (LV) systolic function
- Diastolic dysfunction
- Renal failure
- Pre-existing volume overload



Conclusion

Deficiency of vitamin K dependent clotting factors

Life-threatening bleeding

- Stop warfarin
- Give PCC 40 – 60 ml
- Supplemented with vitamin K 10 mg IV
- Repeat both if necessary, depending on clinical condition and INR

Reversal of warfarin

When available, modern PCCs are recommended over FFP as they provide more consistent and rapid normalization of the INR with an improved safety profile

- Makris M et al. Thrombosis and Haemostasis 1997; 77: 477–480.
- Pabinger I et al. Journal of Thrombosis and Haemostasis 2008; 6: 622–631.
- Yasaka M et al. Thrombosis Research 2005; 115: 455–459.
- Cartmill M et al. British Journal of Neurosurgery 2000; 14: 458–461.

Prothrombin complex concentrate

The infusion of 20-60 mL (500 - 1500 IU) of PCC

- Can be accomplished within 15 minutes
- Without risk of volume overload
- Without apparent risk of thrombotic complications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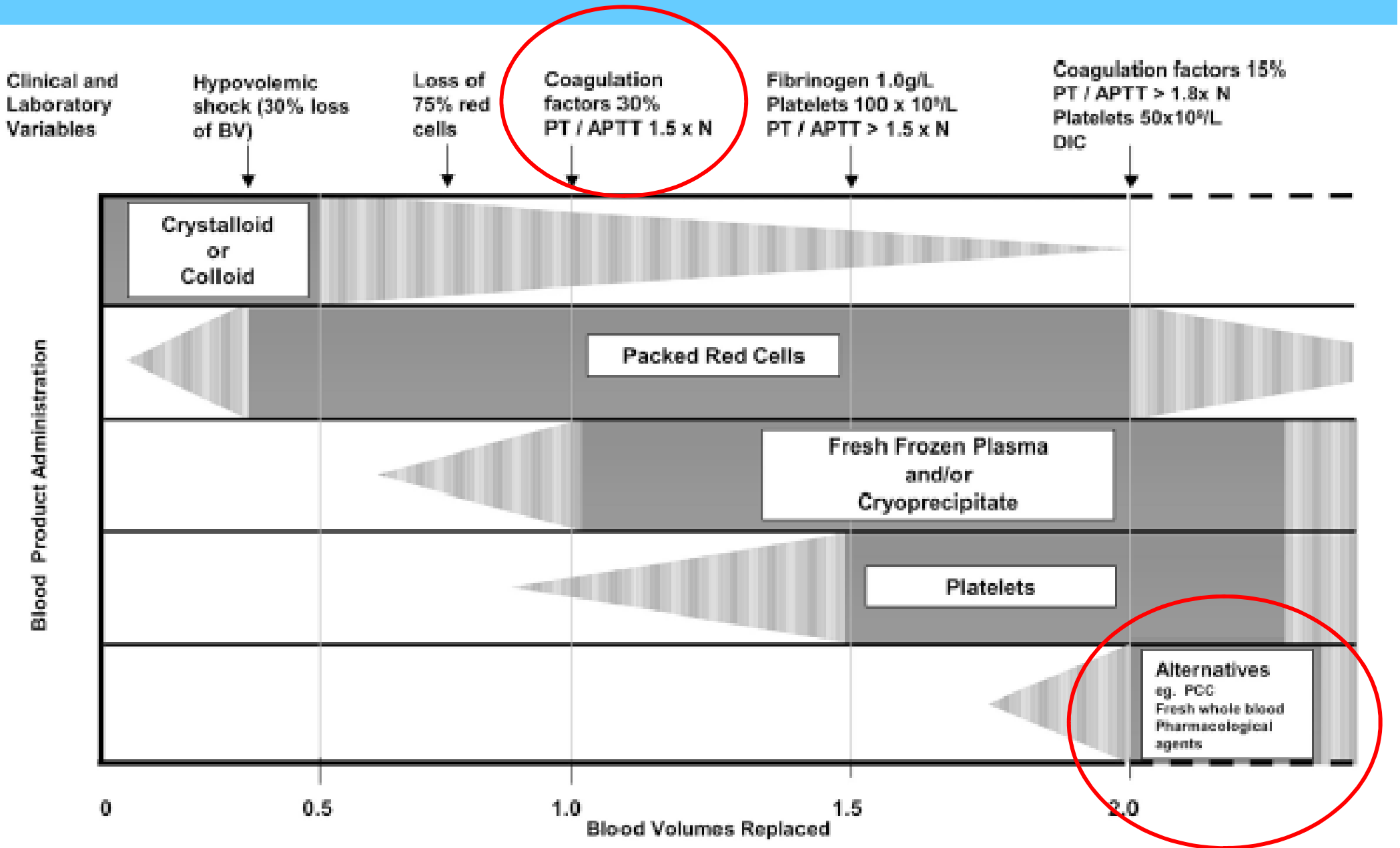
LYNX

Massiivi transfuusio elektiivisessä kirurgiassa (Science 2002; 27)



Warfarin and clotting factor levels at target INR level

- Warfarin reduces the activity of the vitamin K-dependent coagulation factors to varying degrees
  - Factor IX at 40-50%
  - Factor VII at 30%
  - Factor (II) at 20%
  - Factor X at 10% of normal

Sorensen B et al. Blood Coagulation and Fibrinolysis 2003:4:469–77