Substitution Therapy of a Dilutional Coagulopathy and Organ Trauma by Coagulation Factor Concentrates

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The Lethal Triad in Trauma

Acidosis ————

Hypothermia

• BLEEDING
• ORGAN DYSFUNCTION
• DEATH

Coagulopathy
Coagulopathy and Acquired Bleeding

Wounding by trauma / major surgery

Blood loss

Dilutional Coagulopathy

Decreased Enzymes (Coagulation Factors)

Decreased Substrate (Fibrinogen)

Life threatening blood loss

Death

Volume Substitution, Substitution with EC, TC, FFP, Cryo,...

What to substitute?
Clinics of Bone Injury

- Severe bleeding
- Difficult to manage
- High mortality (especially with pelvic ring fracture)
- Preferentially venous bleed
Dilutional Coagulopathy and Bone Bleeding Injury: Pig Model

- Anaesthetized domestic pigs weighing 25-30 kg
- Dilutional coagulopathy by fractionated blood withdrawal and substitution by hydroxy ethyl starch (HES)
- Preparation of the femur
- 3 mm hole drilled into the spongiosa containing region of the femur neck
- Measurement of blood loss and time to hemostasis
Dilutional Coagulopathy and Bone Injury in Pigs
- Study Design -
Characterisation of the Coagulation Deficit

Coagulation abnormalities defined by:

- Thromboelastography (ROTEM)
  - EXTEM: Reaction started with tissue factor
  - FIBTEM: Thrombocyte contribution to TEG suppressed
- Single coagulation factor assays
- Prothrombin time (Global coagulation test)
- Platelet number / function
  - Adhesion
  - Aggregation
Principle of Thromboelastography (TEG)

Blood or plasma + activators → Continuous assessment of blood clot firmness
Thromboelastography - ROTEM -

- clot firmness
- clot formation time (sec) CF (r-time)
- clotting time (sec)
- maximum clot firmness MCF (MA)
- angle ($\alpha$) or maximal Velocity (maxVel)
- clot firmness LI fibrinolysis
- clot formation time (sec) CFT (k-time)
- time
Effect of Fibrinogen Concentrate Application to a Patient with Congenital Fibrinogen Deficiency on TEG

Baseline 15 min 120 min 65 h

< 20 mg/dl 75 mg/dl 130 mg/dl 42 mg/dl

Fibrinogen Plasma Levels
ROTEM Thromboelastography in Pigs

fibTem

Baseline
CT: 52 s CFT: 49 s
α: 81° MCF: 41 mm

dilution
CT: 103 s CFT: - s
α: -° MCF: 6 mm
Porcine Dilutional Coagulopathy: Abnormalities in Thromboelastography (ROTEM)
Platelet Adhesion in Whole Blood

**Baseline**

Surface coverage

15.1 ± 1.5%

**Dilution**

Surface coverage

7.5 ± 2.5%

120 min.
Dilutional Coagulopathy Affects all Components of the Coagulation

- Fibrinogen

- Enzymes/Proenzymes of the coagulation cascade

- Thrombocytes
  - Decreased numbers and impaired function (adhesion and aggregation)
Coagulation Factors in Dilutional Coagulopathy

- Fibrinogen (activity)
- Factor II
- Factor V
- Factor VII
- Factor VIII
- Factor IX
- Factor X
- Factor XI
- Factor XII
- Factor XIII
- AT III
- vWF antigen
- vWF Ristocetin cofactor (activity)

% of Baseline (120 min.)
Coagulation Factor Substitution

- Fibrinogen concentrate - Haemocomplettan® P (125 mg/kg)
- Prothrombin Complex Concentrate (PCC)* - Beriplex® P/N (30 U/kg)
- Negative control (without dilution)
- Dilution control

*Coagulation factors II, VII, IX and X
Fibrinogen Plasma Levels

- dilution
- PCC 30U/kg
- PCC 30 U/kg + fibrinogen 125 mg/kg
- negative control
Factor X Plasma Levels

- dilution
- PCC 30U/kg
- PCC 30 U/kg + fibrinogen 125 mg/kg
- negative control

% of Baseline

minutes

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Prothrombin Time after Substitution with PCC

- Baseline
- Dilution
- PCC

p < 0.02
TEG: Maximal Clot Firmness - fibTEM

Baseline

Dilution

Haemocomplettan

mm

p < 0.05
TEG: Maximal Velocity (120 min)

![Graph showing TEG results for different controls and treatments.](image)

- **neg. Control without dilution**
- **pos. Control dilution**
- **PCC**
- **PCC + fibrinogen**

*p < 0.0001*
Box Plots of Blood Loss after Femur Drill Trauma

Blood loss (ml)

p = 0.0017
Kaplan-Meier Plot of Time to Hemostasis after Femur Drill Trauma

![Graph showing Kaplan-Meier Plot with time to hemostasis (minutes) on the x-axis and proportion of animals on the y-axis. The plot compares negative control, dilution, and Beriplex P/N groups. The p-value is 0.0011.](image)

*) Number of risk, ⊗ denotes censored observations

- □□□ Neg. control (N=5, censored=0)
- ⊗⊗⊗ Dilution (N=7, censored=2)
- ●●●● Beriplex P/N (N=7, censored=0)

p = 0.0011
PCC and Fibrinogen: Time to Hemostasis

![Graph showing time to hemostasis for different treatments: Dilution, Dilution + PCC 30 U/kg, and Dilution + PCC 30 U/kg + Fibrinogen 125 mg/kg.](image)
PCC and Fibrinogen: Blood Loss

- Dilution
- Dilution + PCC 30 U/kg
- Dilution + PCC 30 U/kg + Fibrinogen 125 mg/kg
Summary and Conclusion

• Dilutional coagulopathy after trauma or major surgery results in acquired bleeding with a substantial blood loss from the affected organs.

• Whereas the substitution therapy with PCC leads to a normalization of coagulation enzymes, the substitution with fibrinogen will replenish the substrate of coagulation.

• Combination of PCC and fibrinogen can correct acquired bleeding from bone injury and prevents blood loss.

• Reliable diagnostic tools are needed for a quick examination of the patient’s coagulation status for a evidence-based substitution therapy (point of care concept).