Role of fibrinogen concentrate in coagulation management in complex cardio-vascular surgery

Niels Rahe-Meyer
Clinic for Anaesthesiology and Intensive Care Medicine
In major blood loss, fibrinogen deficiency develops first

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<td>Fibrinogen</td>
<td>1.0 g/L</td>
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Fibrin formation is more impaired than thrombin generation and platelets immediately following cardiac surgery

Effect of thrombin dose on clotting time

Jaques J Physiol 1941

Clotting time [sec]

Thrombin [units]

80% effect
Effect of fibrinogen level on clot firmness

What is the target?

- Increases in fibrinogen increase plasma clot **strength linearly** up to 300 mg/dl
- Plasma clot strength is equal to whole blood at **625 mg/dl**
Correlation blood loss – pre-operative fibrinogen, CABG, RCT, placebo-controlled double blind, n=20


Figure 2: Postoperative bleeding (mean ± SD) in the FIB group (n=10) and in the control group (n=10). There was a significant difference between the mean value in the two groups (p=0.010, Student t-test).
Study design RCT

- Study sponsored by CSL Behring
- Monocentric, 61 patients
- Elective TAAA, ascending aorta, aortic arch
- Double-blinded/placebo controlled
- Strict coagulation treatment algorithm, with the trigger of peri-operative bleeding
- Individually dosed high level fibrinogen
Methods
Target plasma level of fibrinogen

Fibrinogen (g/L)  | 3.6 g/L
---|---
Despotis 2000  | 0.75
ASA Task Force 2006  | 0.8
Spahn 2007  | 1
Weinkove 2008  | 1.5
Fenger-Eriksen 2008  | 2
Rahe-Meyer 2009  | 3.6 g/L ≈ 22 mm FIBTEM
ROTEM® FIBTEM-guided administration of fibrinogen concentrate

CPB, cardiopulmonary bypass; MCF, maximum clot firmness
ROTEM® FIBTEM-guided administration of fibrinogen concentrate

After CPB

Before therapy

Fibrinogen dose [g] = \frac{(target – FIBTEM MCF [mm]) \times (bodyweight [kg]/70)}{2}

CPB, cardiopulmonary bypass; MCF, maximum clot firmness
Thoraco-abdominal aorta
Standardized treatment trigger
5–min bleeding mass

1. After weaning from CPB
2. After heparin reversal (protamine)
3. After surgical haemostasis
Intra-operative bleeding after protamin and surgical haemostasis
Standardized treatment trigger
5–min bleeding mass
Algorithm

Removal from CPB, Protamine, Surgical haemostasis

No treatment

Bleeding 60–250g

No

Yes

Treat as randomised

Fibrinogen

Placebo

No treatment

Bleeding 60–250g

No

Yes

Standardised treatment regimen

CPB, cardiopulmonary bypass

Franziskus Hospital | Hannover Medical School

Niels Rahe-Meyer 2012
Results
Distribution of operations

Fib, fibrinogen concentrate, human; TAAA, thoraco-abdominal aortic aneurysm

Rahe-Meyer et al. Manuscript accepted: Anesthesiology
Fibrinogen levels over time

Clauss Assay

Solomon C et al. Manuscript submitted
Safety

Adverse events

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Events of special interests:

- Thromboembolic or haemorrhagic
- Re-operation because of bleeding
- Allergic or other reactions to IMP or transfusion (TRALI)
- Organ failure or paraplegia

Data given as number of patients (%); AEs, adverse events; Fib, fibrinogen concentrate
## Safety

### Adverse events

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### Fatal AEs

- **Operative haemorrhage**
  - Day 0
- **Cardio-respiratory arrest**
  - Day 1
- **Cerebral haemorrhage**
  - Day 1
- **Cerebral Infarction**
  - Day 1

Myocardial infarction
- Day 30
Reduction of bleeding by treatment

A

Change in rate of bleeding (mL/5 min)

Rate of bleeding before therapy (mL/5 min)

-200
-150
-100
-50
0
50
100

Fibrinogen concentrate
One transfusion cycle
Placebo
Two transfusion cycles
Reduction of bleeding by treatment

Fibrinogen concentrate
Placebo
One transfusion cycle
Two transfusion cycles

Placebo
4FFP or 2PC
4FFP and 2PC
Fibrinogen

Change in rate of bleeding (mL/5 min)
Rate of bleeding before therapy (mL/5 min)
Total of units of allogeneic blood (RBC, FFP, PC) within 24 h

Fib, fibrinogen concentrate; TAAA, thoraco-abdominal aortic aneurysm

Rahe-Meyer et al. Manuscript accepted: Anesthesiology
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*\(p < 0.0001\) for treatment difference using the unstratified Hodges-Lehmann point estimate and corresponding non-parametric confidence intervals; Fib, fibrinogen concentrate; TAAA, thoraco-abdominal aortic aneurysm

Rahe-Meyer et al. Manuscript accepted: Anesthesiology
Secondary endpoint
Patients with transfusion

Rahe-Meyer et al. Manuscript accepted: Anesthesiology
Secondary endpoint
Patients with transfusion

- **Allogeneic group**: 100%
- **Fibrinogen group**: 55%

*p < 0.0001*  
*2-sided non-parametric Wilcoxon/Mann Whitney rank sum test*  

**Total avoidance of transfusion**

- **Allogeneic group**: 0%
- **Fibrinogen group**: 45%

Rahe-Meyer et al. Manuscript accepted: Anesthesiology
Conclusions

ESA guidelines:
Management of severe perioperative bleeding (publication anticipated end of 2012)

Fibrinogen concentrate infusion guided by point-of-care viscoelastic coagulation monitoring may be used to reduce perioperative blood loss in complex cardiovascular surgery (level of evidence 1+; grade of recommendation B).