Massive obstetric Haemorrhage
Lessons from trauma & novel strategies
Is fibrinogen concentrate our new saviour?

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No conflict of interest
Massive obstetric haemorrhage: a major issue in public health

- 1.25/1000 deliveries

- Still one of the leading cause of maternal death, even in high resource countries
  Hogan MC et al. Lancet 2010

- 80% potentially preventable
  CMACE
  French Confidential Enquiry into maternal death
Massive obstetric haemorrhage: no common definition

- A blood loss of 2500mL or more
- Transfusion of 5 units of red blood cells or more
- Need for an haemostatic intervention
- Treatment of a coagulopathy

Wise A. Clark V. Curr Opin Anaesthesiol 2008
Brace V. et al. BJOG 2007
Coagulopathy in traumatic haemorrhage

Hess JR et al., J Trauma 2008
Brohi K, J R Army Med Corps 2009
Lessons from trauma

New therapeutics proposed to deal with this coagulopathy

- FFP RBC ratio close to 1 for 1
- Fibrinogen concentrate
- Tranexamic acid
The critical role of fibrinogen in clot formation

Fibrinogen is the first parameter to decrease during massive bleeding.

- Hiipala ST et al., Anesth Analg 1995
monocentric retrospective cohort of 18501 women
Major PPH: n=456

Fibrinogen levels correlated the best with blood loss and felt progressively as volume increased.
The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage

B. CHARBIT,*† L. MANDELBROT, † E. SAMAIN,§ G. BARON,¶ B. HADDAOUİ, †† H. KEITA, †¶ O. SİBONY,** D. MAHIEU-CAPUTO,¶ M. F. HURTAUD-ROUX,** M. G. HUISSE, ¶¶¶ M. H. DENNINGER, †††† and D. DE PROST†††† FOR THE PPH STUDY GROUP

Retrospective cohort of 128 parturients with PPH requiring prostaglandins

Fibrinogen ≤2g/L: PPV for severe PPH 100%
Fibrinogen >4g/L: NPV for severe PPH: 80%

Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes

C. Rourke,* 1  N. Curry,* 1  S. Khan, *  R. Taylor, †  I. Raza, *  R. Davenport, *  S. Stanworth, † and K. Brohi*
Prospective cohort study of 517 trauma patients
Admission level of fibrinogen: not a significant predictor of major blood loss
an independent predictor of mortality at 24h and 28 days

Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes


Fibrinogen level

24h

28 days

Alive

Dead

Alive

Dead

No cryoprecipitate in the first 12h

Cryoprecipitate in the first 12h
Prospective cohort study of 517 trauma patients

Admission level of fibrinogen: not a significant predictor of major blood loss

an independent predictor of mortality at 24h and 28 days
What does it mean?

• The association between low fibrinogen plasma concentration and PPH severity or mortality in trauma has been demonstrated.

But

• It does not mean that compensation for this low fibrinogen plasma concentration improve patients outcomes.
Fibrinogen therapy

• Usually given as cryoprecipitate:
  – potential viral contamination
  – variable concentration of Fg

  Sorensen B & Bevan D, BJH 2010

• Increasing use of pasteurized fibrinogen concentrate

<table>
<thead>
<tr>
<th>Product</th>
<th>Quantity needed to increase Fg plasma concentration of 1g/L</th>
<th>Cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>4 units=1000mL</td>
<td>452</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>13 units=260mL</td>
<td>563</td>
</tr>
<tr>
<td>Fibrinogen concentrate</td>
<td>2g=100mL</td>
<td>518</td>
</tr>
</tbody>
</table>
Fibrinogen concentrate

- Immediatly available for reconstitution
- No need for thawing or blood group matching
- Efficacy and safety proved in congenital fibrinogen deficiencies

What is the evidence concerning its use in bleeding patients?

Evidence from experimental studies on fibrinogen concentrate efficacy in massive bleeding
Whole blood of healthy individuals (n=20) Haemodilution of 55% with saline, HES, dextran

Ex vivo addition of Fg concentrate

Whole blood clot formation profiles recorded using thromboelastometry

Ex vivo addition of Fg concentrate improved the coagulopathy induced by all the 3 plasma expanders tested.
Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model

D. Fries¹*, A. Krismer¹, A. Klingler², W. Streif³, G. Klima⁴, V. Wenzel¹, T. Haas¹ and P. Innerhofer¹

1- Withdraw of 65% of blood volume in 14 pigs, replaced by gelatin solution
2- Randomisation: 250mg/kg fibrinogen or normal saline
3- Liver injury
   ➔ Normalisation of ROTEM parameters (except CT) with fibrinogen
   ➔ Electron microscopic scan

Bleeding (mL)

NaCl 0,9%: 2010 mL [1800-2200]  Fibrinogen: 1100 mL [800-1400]
Evidence from clinical studies on fibrinogen efficacy and safety in bleeding patients
Retrospective chart review of 252 patients at a US Army combat support hospital

>10RBCs in 24h

Fg:RBC ratio independently associated with mortality:

OR 0.37 (95%CI 0.17-0.81)
Use of thromboelastometry-guided Fibrinogen in trauma bleeding patients

Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients

Retrospective reviews of single centre experiences

Significant decrease in 30-day mortality

Significant reduction in exposure to allogeneic blood products
Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review

Sibylle Kozek-Langenecker¹*, Benny Sørensen²,³, John R Hess⁴ and Donat R Spahn⁵

- Systematic review investigating the current evidence for the use of FFP and Fg concentrate in the perioperative or trauma setting

- Inclusion criteria: studies from all types, reporting an outcome of the administration of FFP or Fg concentrate within the perioperative or massive trauma setting (1999-2010).
Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review

Sibylle Kozek-Langenecker\textsuperscript{1}, Benny Sørensen\textsuperscript{2,3}, John R Hess\textsuperscript{4} and Donat R Spahn\textsuperscript{5}

\begin{itemize}
  \item 3 RCT, 2 prospective cohort studies, \textbf{16 retrospective studies and case reports}
  \item No comparator studies in patients with haemorrhage due to massive trauma or obstetric haemorrhage
\end{itemize}
The desperate need for good-quality clinical trials to evaluate the optimal source and dose of fibrinogen in managing bleeding

Simon J Stanworth¹ and Beverley J Hunt*²,³

- Current evidence: mainly case series and uncontrolled studies
- Does not support the superiority of one source of fibrinogen over another
Efficacy of fibrinogen concentrate in bleeding patients: randomized controlled trials performed in the context of perioperative bleeding
Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial

- Randomized controlled trial
- Radical cystectomy (n=20)
- Dilution level 30%, randomisation in fg concentrate (45mg/kg) or placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fg</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Loss</td>
<td>2933 ±1320</td>
<td>2682 ±962</td>
<td>0.40</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td>2.5 (0-6)</td>
<td>2 (0-5)</td>
<td>0.91</td>
</tr>
<tr>
<td>Postop (48H)</td>
<td>1.5 (0-2)</td>
<td>0 (0-2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>total</td>
<td>4.0 (0-6)</td>
<td>3.5 (0-5)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Fg significantly improved MCF and reduced postoperative but not total transfusion requirement. No difference in blood loss.
Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery

A prospective randomised pilot study

Martin Karlsson¹; Lisa Ternström¹; Monica Hyllner²; Fariba Baghaei³; Agneta Flinck⁴; Stanko Skrtic⁵; Anders Jeppsson¹

• RCT: 20 CABG patients with preoperative plasma Fg levels < 3.8g/L

• Randomisation: 2g Fg concentrate vs no infusion before surgery

• Primary endpoint: safety with clinical adverse events and graft occlusion assessed by multi-slice computed tomography
Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery

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one subclinical vein graft occlusion in the FIB group.

In the Fg concentrate infusion group, postoperative blood loss was reduced by 32%
(565±150 ml vs 830 ±268 mL/12h, p=0.010)
Elective thoracic or thoraco-abdominal aortic replacement surgery with CPB

Clinically relevant coagulopathy immediately after the removal of CPB

Randomisation (n=80)

Target FIBTEM MCF: 22mm (i.e. 3.6 g/L)

Fibrinogen
- N=38
- Dosing according to the FIBTEM

Placebo
- N=42

If bleeding continues standardized transfusion protocol followed

Exclusion of patients with anticoagulant therapy, redux, acquired coagulation disorders

Exclusion if bleeding >250g
### Effects of Fibrinogen Concentrate as First-line Therapy during Major Aortic Replacement Surgery

**A Randomized, Placebo-controlled Trial**

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen concentrate (n=29)</th>
<th>Placebo (n=32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nb of allogeneic blood components within the first 24h (IQR)</td>
<td>2 (0-8)</td>
<td>13 (8-21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nb of patients with total avoidance of allogeneic blood components n(%)</td>
<td>13 (45%)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nb of ICU-free days</td>
<td>43 (40-44)</td>
<td>43 (41-44)</td>
<td>ns</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>mortality</td>
<td>1</td>
<td>4</td>
<td>ns</td>
</tr>
</tbody>
</table>

Fibrinogen concentrate administered intraoperatively as targeted first line haemostatic intervention reduces the need for transfusion of allogeneic blood products in patients undergoing major aortic surgery.

Need to be confirmed in larger multicentric RCT with ITT
The evidence on fibrinogen efficacy in bleeding patients

- Only 3 randomized controlled trials
- of small sample size (101 patients in all)
- involving bleeding patients in the context of scheduled surgery
- No benefit in terms of transfusion requirement in 2 studies
...and what about fibrinogen concentrate in massive obstetric haemorrhage?
Differences between obstetric and trauma haemorrhage

**Obstetric haemorrhage**
- One source of bleeding
- Controlled environment
- Higher Fg baseline plasma level

**Trauma bleeding**
- Multiple sources of bleeding
- External initial environment
- Normal Fg baseline plasma level
Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations

C. Fenger-Eriksen¹, M. Lindberg-Larsen¹, A. Q. Christensen¹, J. Ingerslev¹* and B. Sørensen¹ ²

- Retrospective study
- N=43 patients with massive haemorrhage
- 12 obstetric cases

<table>
<thead>
<tr>
<th></th>
<th>Before Fg substitution</th>
<th>After Fg substitution</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood loss</td>
<td>4000 mL</td>
<td>50 mL</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Br J Anaesth 2008; 101: 769–73*
• Obstetric cases: 30% (placental abruptio)
• 46% bleeding stopped with blood components and Fg alone.

The use of fibrinogen concentrate to correct hypofibrinogenenaemia rapidly during obstetric haemorrhage

S.F. Bell, R. Rayment,* P.W. Collins* R.E. Collis
Department of Anaesthesia and *Department of Haematology, University Hospital of Wales, Cardiff, UK


• 6 cases of obstetric haemorrhage with hypofibrinogenemia
• Successfully treated with Fg concentrate in conjunction with other blood products and obstetric intervention
Fibrinogen in obstetric haemorrhage

• In total, only 144 cases of severe obstetric haemorrhage with massive transfusion and fibrinogen substitution are described

• Only case reports or cases series

• Very low level of evidence
The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial

First randomised controlled study investigating the use of fibrinogen concentrate in obstetric haemorrhage

Objective: to evaluate whether initial treatment with fibrinogen concentrate reduces the need for allogenic blood transfusion in PPH

Design: multicentre placebo-controlled randomised double-blind clinical trial
Caesarean section

Blood loss ≥1000mL

Manual removal of placenta & blood loss ≥500mL

Exploration of the uterine cavity & blood loss ≥1000mL

Baseline blood samples & status

Randomisation

2g Fg concentrate

100mL isotonic saline

blood samples & status at 15min, 4h, 24h

6 weeks follow up

Exclusion criteria:
- Unable to give informed consent
- Inherited coagulation deficiencies
- Anti-thrombotic treatment
- Pre-pregnancy weight <45kg

The FIB-PPH trial
The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial

Setting: started in June, 2011 in 4 university-affiliated public hospitals (Copenhagen area), 107 patients in each group for a reduction of transfusion risk of 33%, inclusion over

Primary outcome: need for transfusion with allogenic blood products

Secondary outcomes: severe PPH, estimated blood loss, total amount of blood transfused, rebleeding, Hb<5.8g/dL

Potential side effects: fever, headache, nausea vomiting, allergic reactions, thromboembolic complications

2 sub groups analysis planned: according to the mode of delivery and to the existence of a baseline hypofibrinogenemia
Adverse events associated with fibrinogen concentrate infusion
Thrombotic complications?

• The addition of postpartum bleeding to a delivery increases the risk of postpartum VTE.
  Jacobsen AF et al., JTH 2008

• Elevated plasma fg levels are strongly associated with both arterial and venous thrombotic complications.
  Danesh J et al., JAMA 2005

• Is hyperfibrinogenemia only a biomarker of a proinflammatory state or really a causative mechanism of thrombotic events?
Causal relationship between hyperfibrinogenemia, thrombosis, and resistance to thrombolysis in mice

Kellie R. Machlus,¹ Jessica C. Cardenas,¹ Frank C. Church,¹ and Alisa S. Wolberg¹

Experimental study in mice with increased Fg plasma level

<table>
<thead>
<tr>
<th>Fibrinogen (mg/mL)</th>
<th>2.4</th>
<th>4.4</th>
<th>6.4</th>
</tr>
</thead>
</table>

Hyperfibrinogenemia increased thrombus fibrin content, promoted faster fibrin formation, and increased fibrin network density, strength, and stability.

These data indicate that hyperfibrinogenemia directly promotes thrombosis and thrombolysis resistance, and does so via enhanced fibrin formation and stability.
Perioperative Administration of Fibrinogen is Associated with Increased Risk of Postoperative Thromboembolic Complications after Cardiac Surgery

Carl-Johan Jakobsen¹*, Mariann Tang² and Lars Folkesen¹

All patients undergoing cardiac surgery at Aarhus University Hospital in 2008 and 2009 were obtained from West Denmark Heart Registry (n=1876)

Fibrinogen infusion

Independent risk factor for postoperative stroke

Independent risk factor for postoperative dialysis

Conclusion: Perioperative administration of fibrinogen could be associated with increased risk of neurological thromboembolic complication and renal failure and thus have potential thromboembolic side effects.
Management of bleeding and coagulopathy following major trauma: an updated European guideline

Recommendation 27 We recommend treatment with fibrinogen concentrate or cryoprecipitate in the continuing management of the patient if significant bleeding is accompanied by thromboelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5 to 2.0 g/l. (Grade 1C)

We suggest an initial fibrinogen concentrate dose of 3 to 4 g or 50 mg/kg of cryoprecipitate, which is approximately equivalent to 15 to 20 single donor units in a 70 kg adult. Repeat doses may be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels. (Grade 2C)
Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

Sibylle A. Kozek-Langenecker, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa Alvarez Santullano, Edoardo De Robertis, Daniela C. Filipescu, Dietmar Fries, Klaus Görflinger, Thorsten Haas, Georgina Imberger, Matthias Jacob, Marcus Lancé, Juan Llau, Sue Mallett, Jens Meier, Niels Rahe-Meyer, Charles Marc Samama, Andrew Smith, Cristina Solomon, Philippe Van der Linden, Anne Juul Wikkelsø, Patrick Wouters and Piet Wyffels

Eur J Anaesthesiol 2013; 30:1–112
Considering physiologically elevated fibrinogen concentration in pregnancy, we suggest that a higher trigger value for treating hypofibrinogenenaemia may be required. (grade C)
Fibrinogen concentrate in massive obstetric haemorrhage

- Fg concentrate appears as a promising therapeutic in massive bleeding patients
- It is increasingly being used in the treatment of massive obstetric haemorrhage but still its efficacy is only based on low level of evidence and from settings different from obstetrics.

Unanswered questions:
- Which target fibrinogen concentration?
- What is the optimal dose of fibrinogen?
- Use of different strategies in obstetrics and other bleeding contexts?
Massive obstetric haemorrhage: is fibrinogen concentrate our new saviour?

Too early to give the right answer

- Evidence in favour of the pro-coagulant effect of fibrinogen concentrate, but we need more data on clinical outcomes and adverse events to induce change in practice.

It cannot replace surgical haemostatic interventions.