Injectable hemostatic adjuncts

FIinTIC-Study

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Uncontrolled Bleeding is a Major Cause of Death in Trauma

(Patients dying in-hospital within the first 48 hours after trauma)

Sauaia et al., J Trauma 1995; 38: 185-193
Evans et al., World J Surg 2010; 34: 1720-21
The Incidence of Acute Post-Traumatic Coagulopathy upon ER Admission

(25% of trauma patients are coagulopathic upon ER admission)
The Clinical Significance of Acute Post-Traumatic Coagulopathy: Mortality

- Brohi J Trauma 2003 n=1,088
- MacLeod J Trauma 2003 n=10,790
- Maegele Injury 2007 n=8,724
- Brohi Ann Surg 2007 n=208

Mortality in (%)

- Normal coagulation
- Coagulopathy

x 4.6
### Key Recommendations for the Management of Acute Traumatic Hemorrhage: S3-Guideline „Polytrauma“

**Trauma-induced coagulopathy = „own clinical entity“**
Recommendation 23
We recommend that monitoring and measures to support coagulation be initiated as early as possible (Grade 1C).
The current concept

Coagulopathy of Trauma

Acute Traumatic Coagulopathy (ATC)
(Immediately after injury (endogenous))

- Tissue Trauma
- Hypoperfusion/Shock
- Inflammation
- Sympathoadrenal Activation

Endothelial Activation
Damage
Hyperpermeability

- Protein C-Pathway Activation
- Weibel-Palade Body Degradation
- Glycocalyx Shedding

- TM ↑
- TPA ↑
- Autoheparinization

Hypocoagulation / Fibrinolysis

Iatrogenic Coagulopathy (IC)
(Delayed after injury (exogenous))

Volume Resuscitation
Hemodilution

Depletion of Factors

- Acidosis
- Hypothermia

„Vicious Cycle“

Maegele et al., Shock 2013
The role of fibrinogen

Primary haemostasis:
- Ligand between activated platelets
- GP receptor IIb/IIIa has a high affinity to fibrinogen

Secondary haemostasis
- Precursor for fibrin formation
- Fibrinogen is the substrate of the coagulation process

Mosesson et al. J Thromb Haemost 2005
Reasons for low fibrinogen

- Bleeding
- Consumption
- Dilution
- (Hyper)fibrinolysis
- Hypothermia
- Acidosis

Schlimp CJ, Schöchl H. Haemostasiologie 2014
Normovolaemic hemodilution

![Graph showing changes in fibrinogen and platelets with percentage of original blood volume exchanged.](image-url)

- **Fibrinogen** [mg/dL]
- **Platelets** [$10^9$/L]

% Original blood volume exchanged:
- 10
- 20
- 30
- 40
- 50
- 60
- 70
- 80

McLoughlin et al. Anaesth Anal 1996
Early coagulopathy in trauma:
An on-scene and hospital admission study

On-scene coagulation factor concentrates as a function of injury severity
Fibrinogen: First factor to reach critical levels during severe bleeding replaced with plasma and fluids (Hippala et al., 1995)
Fibrinogen levels at Emergency Room admission and mortality

N = 517

24-hours mortality

28-days mortality

Impact of fibrinogen levels on outcome after acute injury in patients with massive transfusion.


+ Author information

Abstract

BACKGROUND: For critically injured patients requiring a massive transfusion, the optimal plasma fibrinogen level is unknown. The purpose of this study was to examine the impact of the fibrinogen level on mortality. We hypothesized that decreasing fibrinogen levels are associated with worse outcomes.

STUDY DESIGN: All patients undergoing a massive transfusion from January 2000 through December 2011 were retrospectively identified. Those with a fibrinogen level measured on admission to the surgical ICU were analyzed according to their fibrinogen level (normal [≥180 mg/dL], abnormal [≥101 to <180 mg/dL], and critical [≤100 mg/dL]). Primary outcome was death. Multivariate analysis evaluated the impact of fibrinogen on survival.

RESULTS: There were 260 patients who met inclusion criteria. Ninety-two patients had normal admission fibrinogen levels, 114 had abnormal levels, and 54 patients had critical levels. Patients with a critical fibrinogen level had significantly higher mortality at 24 hours compared with patients with abnormal (31.5% vs 5.3%; adj. p < 0.001) and normal fibrinogen levels (31.5% vs 4.3%; adjusted p < 0.001). Patients with a critical fibrinogen level had significantly higher in-hospital mortality compared with patients with abnormal (51.9% vs 25.4%; adjusted p = 0.013) and normal fibrinogen levels (51.9% vs 18.5%; adjusted p < 0.001). A critical fibrinogen level was the most important independent predictor of mortality (p = 0.012).

CONCLUSIONS: For patients undergoing a massive transfusion after injury, as the fibrinogen level increased, a stepwise improvement in survival was noted. A fibrinogen level ≤100 mg/dL was a strong independent risk factor for death. The impact of an aggressive fibrinogen replacement strategy using readily available products warrants further prospective evaluation.

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<th>Fibrinogen Level</th>
<th>24 h Mortality</th>
<th>In-hospital Mortality</th>
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<tr>
<td>&gt;180 mg/dL</td>
<td>4.3</td>
<td>18.5</td>
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<tr>
<td>101-180 mg/dL</td>
<td>5.3</td>
<td>25.4</td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
<td>31.5</td>
<td>51.9</td>
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</table>
The role of Fibrinogen

- Substrate for clotting (converted into fibrin by thrombin)!
The role of Fibrinogen

Maegele, Textbook of Surgery 2014 (in press)
Impact of fibrinogen on maximum clot firmness / stability

Absolute strength of the clot is reflected by amplitude in mm

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<thead>
<tr>
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<td>CFT: 76s</td>
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<td>A10: 60mm</td>
<td>A20: 67mm</td>
<td>MCF: 71mm</td>
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<td>CT: 45s</td>
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<tr>
<td>A10: 17mm</td>
<td>A20: 18mm</td>
<td>MCF: 20mm</td>
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</table>

Clotting → interaction of platelets, fibrin, aFXIII

aFXIII, activated factor XIII; CFT, clot formation time; CT, clotting time; MA, maximum amplitude; MCF, maximum clot firmness
Low MCF/MA is associated with increased blood loss, blood transfusion requirement and higher mortality

FIBTEM examples of normal, saline diluted and substituted clots

FIBTEM baseline

33% Dilution with Saline

Saline Dilution + Fibrinogen

Saline Dilution + FXIII

Saline Dilution + Fib + FXIII
Fibrinogen in the treatment of post-traumatic coagulopathy

Electronmicroscopic findings

Normal clotting

Diluted clot after administration of fibrinogen

Dilution

Fries et al., Br J Anaesth 2005
Coagulation parameters and their values to predict massive transfusion

| Table 4 Coagulation parameters and their prediction of massive transfusion (MT) |
|-------------------------------|------------------|------------------|------------------|
| **FIBTEM MCF**                | 0.84 (0.79 to 0.88) | ≤7 mm            | 77.5 (66.8 to 86.1) |
| **FIBTEM A10**                | 0.83 (0.78 to 0.87) | ≤4 mm            | 63.3 (51.7 to 73.9) |
| **EXTEM CT**                  | 0.71 (0.66 to 0.76) | ≤72 s            | 76.3 (65.2 to 85.3) |
| **EXTEM CFT**                 | 0.74 (0.68 to 0.79) | ≤147 s           | 64.5 (52.7 to 75.1) |
| **EXTEM MCF**                 | 0.76 (0.71 to 0.81) | ≤52 mm           | 67.1 (55.4 to 77.5) |
| **INTEM CT**                  | 0.71 (0.65 to 0.76) | ≤167 s           | 65.3 (53.1 to 76.1) |
| **INTEM CFT**                 | 0.78 (0.73 to 0.82) | ≤111 s           | 75.0 (63.4 to 84.5) |
| **INTEM MCF**                 | 0.78 (0.73 to 0.83) | ≤51 mm           | 61.6 (49.5 to 72.8) |
| **Platelet count**            | 0.70 (0.65 to 0.75) | ≤161 × 10^9/μL   | 62.0 (50.4 to 72.7) |
| **Quick value**               | 0.87 (0.83 to 0.90) | ≤60%             | 84.0 (75.0 to 91.9) |
| **aPTT**                      | 0.85 (0.81 to 0.89) | ≤35.2 s          | 71.6 (59.9 to 81.5) |
| **Fibrinogen concentration**  | 0.83 (0.78 to 0.87) | ≤148 mg/dL       | 84.2 (74.0 to 91.5) |

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ROC-AUC (95% CI)</th>
<th>Optimum threshold (for best sensitivity and specificity)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>0.87 (0.83 to 0.91)</td>
<td>≤10.1 g/dL</td>
<td>77.5 (66.8 to 86.1)</td>
<td>685 (79.3 to 88.9)</td>
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<tr>
<td>Base deficit</td>
<td>0.76 (0.76 to 0.86)</td>
<td>≤6.3</td>
<td>69.6 (57.3 to 80.1)</td>
<td>798 (73.3 to 85.3)</td>
</tr>
<tr>
<td>pH</td>
<td>0.76 (0.70 to 0.81)</td>
<td>≤7.276</td>
<td>62.3 (49.8 to 73.7)</td>
<td>80.0 (73.6 to 85.4)</td>
</tr>
<tr>
<td>Lactate</td>
<td>0.74 (0.69 to 0.79)</td>
<td>≤4.18 mmol/L</td>
<td>54.9 (42.7 to 66.8)</td>
<td>88.0 (82.9 to 92.0)</td>
</tr>
</tbody>
</table>

A10, clot amplitude 10 minutes after CT; aPTT, activated partial thromboplastin time; CFT, clot formation time; CI, confidence interval; CT, clotting time; EXTEM, extrinsically activated thromboelastometric test; FIBTEM, extrinsically activated thromboelastometric test with cytochalasin D; INTEM, intrinsically activated thromboelastometric test; MCF, maximum clot firmness; ROC-AUC, area under the receiver operating characteristic curve.
what does the literature say?


**Fibrinogen concentrates for bleeding trauma patients: what is the evidence?**

Meyer MA, Ostrowski SR, Windeløv NA, Johansson PI.

**METHODS:** PubMed and Cochrane database search, 'fibrinogen' and ('concentrate' or 'trauma'), not 'congenital', 10 years.

**RESULTS:** Only four papers were identified. None were randomized controlled trials. The main conclusion of these papers was that administration of fibrinogen sometimes together with prothrombin complex concentrate might improve haemostasis in trauma patients resuscitated with synthetic colloids.

**Conclusion** Evidence for the use of fibrinogen concentrate to trauma patients with massive bleeding is lacking. Well-designed prospective, randomized, double-blinded studies evaluating the effect of fibrinogen concentrate, as the only intervention, are urgently needed.


**The desperate need for good-quality clinical trials to evaluate the optimal source and dose of fibrinogen in managing bleeding.**

Stanworth SJ, Hunt BJ.

**Is fibrinogen the answer to coagulopathy after massive transfusions?**

Samuel A Tisherman®
Fibrinogen depletion in trauma: early, easy to estimate and central to trauma-induced coagulopathy.

Davenport R, Brohi K.

Author information

Abstract
Fibrinogen is fundamental to hemostasis and falls rapidly in trauma hemorrhage, although levels are not routinely measured in the acute bleeding episode. Prompt identification of critically low levels of fibrinogen and early supplementation has the potential to correct trauma-induced coagulopathy and improve outcomes. Early estimation of hypofibrinogenemia is possible using surrogate markers of shock and hemorrhage; for example, hemoglobin and base excess. Rapid replacement with fibrinogen concentrate or cryoprecipitate should be considered a clinical priority in major trauma hemorrhage.
Management of bleeding and coagulopathy following major trauma: an updated European guideline

Donat R Spahn\textsuperscript{1}, Bertil Bouillon\textsuperscript{2}, Vladimír Cerný\textsuperscript{3,4}, Timothy J Coats\textsuperscript{5}, Jacques Duranteau\textsuperscript{6}, Enrique Fernández-Mondéjar\textsuperscript{7}, Daniela Filipescu\textsuperscript{8}, Beverley J Hunt\textsuperscript{9}, Radko Komadina\textsuperscript{10}, Giuseppe Nardi\textsuperscript{11}, Edmund Neugebauer\textsuperscript{12}, Yves Ozié\textsuperscript{13}, Louis Riddez\textsuperscript{14}, Arthur Schultz\textsuperscript{15}, Jean-Louis Vincent\textsuperscript{16} and Rolf Rossaint\textsuperscript{17}

Fibrinogen and cryoprecipitate

\textbf{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)
# Substitution: Fib-Concentrate vs FFP vs Cryo

## Fibrinogen Dose Calculator

<table>
<thead>
<tr>
<th>Patient Information</th>
<th>Value</th>
<th>Unit</th>
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</thead>
<tbody>
<tr>
<td>Body Weight</td>
<td>85</td>
<td>kg</td>
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<tr>
<td>Hematocrit</td>
<td>25%</td>
<td>%</td>
</tr>
<tr>
<td>Plasma Volume</td>
<td>3485</td>
<td>ml</td>
</tr>
<tr>
<td>Blood Volume</td>
<td>4647</td>
<td>ml</td>
</tr>
</tbody>
</table>

| Baseline Fib Concentration | 0.8  | g/l  |
| Target Fib Concentration  | 1.7  | g/l  |

### Concentration of Fibrinogen in Product

- **FFP Concentration**: 2.3 g/l
- **Cryo Concentration**: 12 g/l
- **FibCon Concentration**: 20 g/l

### Volume of Product per Unit

- **FFP Volume per unit**: 250 ml
- **Cryo Volume per unit**: 125 ml
- **FibCon Volume per unit**: 50 ml

### Dose Calculation

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>Cryo</th>
<th>FibCon</th>
<th>Units</th>
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<tr>
<td>Dose</td>
<td>28</td>
<td>33</td>
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<tr>
<td>Volume</td>
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<td>412,5</td>
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<tr>
<td>Resultant Fib Concentration</td>
<td>1.70</td>
<td>1.71</td>
<td>1.78</td>
<td>g/l</td>
</tr>
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Fibrinogen in Trauma induced coagulopathy
Study design

- Prospective, randomised, controlled and double-blind Study,
- N = 60 patients
- Early administration of 50 mg/kg BW fibrinogen concentrate versus placebo in bleeding trauma patients.
- Assessment time points:
  - Inclusion (at site of the accident) (T1)
  - Immediately after trauma bay arrival (T2)
  - after 3 hours (T3)
  - after 9 hours (T4)
  - after 24 hours (T5)
  - after 48 hours (T6)
  - after 1 week (T7)
Study aim

✓ Pilot /proof of concept study to investigate the effect of early treatment with fibrinogen concentrate on:

1. Change in plasma coagulation
2. Transfusion requirements/blood loss
3. Thromboembolic complications
4. Clinical endpoint/morbidity/LOS
**Inclusion criteria:**

1. Trauma patient (Age 18-85 years)
2. Patients admitted to a FlinTIC study center
3. Patients with visible or suspected bleeding and state of shock (RRsyst <110 mmHG)
4. Confirmed of bleeding after completed diagnostic procedures (CT)

**Exclusion criteria**

1. Patients with history of or known thombembolic events
2. Patients with survivable trauma/deth at scene
3. Pregnancy
Number of patients:

- 60 patients (30 placebo, 30 verum)
- expected/calculated „drop out rate“: 50%

Patients per emergency vehicle/rescue helicopter:

- 9 patients in 2 years per center

Patienten per hospital

- 12 patients in 2 years per center
Endpoints

**Primary endpoint:**
Fibrinogen polymerisation measure with the FIBTEM® MCF

**Secondary endpoints:**
- Other ROTEM® and biological parameters
- Number of thromboses at 7 days assessed by duplex ultrasound

**Further parameters:**
- Blood loss: documentation of (calculated) blood loss transfusion requirements
- Clinical endpoints
- Volume requirement
- Use of further coagulation products (coagulation factor concentrates, antifibrinolytic agents, DDAVP, buffer therapy, ...).
FGTW: Fibrinogen concentrate, LFB France (1,5 g in 100 mL)

- **Dosage:** 1x 50 mg/kg KG (1 package per 30 kg KG)
- **storage:** room temperature
- Temp range of -20 up to + 40 °C: 6 month
- at room temperature: 3 years
Austria

- Active Center
- Initiated but inactive Center
- Closed Center
- New Initiated Center
## Austria

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<td>H01</td>
<td>Christophorus 1 Innsbruck</td>
<td>Dr. Marc Kaufmann</td>
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<tr>
<td>H03</td>
<td>Christophorus 6 Salzburg</td>
<td>Dr. Bernhard Ziegler</td>
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<td>H06</td>
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<td>Dr. Christine Wimmer</td>
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<td>Dr. Christian Niederwanger</td>
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<td>Univ. Doz. Dr. Michael Baubin</td>
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<td>Dr. Manuel Mauerer</td>
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<tr>
<td>H13</td>
<td>NEF Telfs</td>
<td>Dr. Markus Thaler</td>
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</tbody>
</table>
Germany

G01
Cologne-Merheim Medical Center
Department for Trauma Surgery und Orthopedics
PI & National Coordinator:
Prof. Dr. Marc Maegele

G03
Federal Armed Forces Medical Center Ulm
Department of General, Visceral and Thoracic Surgery
PI: Dr. Thorsten Hauer

Frankfurt / Kempten / Duisburg ??
CERTIFICATE OF APPRECIATION

IS AWARDED TO

COLOGNE-MERHEIM MEDICAL CENTER
DEPARTMENT OF TRAUMA SURGERY AND ORTHOPEDICS
KÖLN, GERMANY

FOR EXCEPTIONAL CONTRIBUTION TO THE COALITION WARFARE PROGRAM PROPOSAL, FIBRINOGEN SUPPLEMENTATION IN TREATING TRAUMA PATIENTS WITH BLEEDING COMPLICATIONS. WORKING IN ASSOCIATION WITH THE UNITED STATES ARMY INSTITUTE OF SURGICAL RESEARCH (USAISR), THE DEPARTMENT OF TRAUMA SURGERY AND ORTHOPEDICS OF COLOGNE-MERHEIM MEDICAL CENTER WAS INSTRUMENTAL IN THE IMPLEMENTATION AND SUCCESS OF THE CLINICAL TRIAL AND REFLECTS GREAT CREDIT UPON THEM.

16 May 2013
USAISR
Fort Sam Houston, TX

Michael A. Weber
Colonel, US Army
Commanding
Czech Republic

C01
University Hospital Hradec Kralove
Department for Anaesthesiology and Intensive Care
PI & National Coordinator: Dr. Anatolij Truhlar

K01
Christoph 06 Hradec Kralove
PI: Dr. Anatolij Truhlar
Denmark

D01
Aarhus University Hospital
Department of Anaesthesiology
PI & National Coordinator:
Dr. Christian Fenger-Eriksen

N01 / H1
Akutlægehelikopter
Karup Lufthavn
PI: Dr. Christian Fenger-Eriksen
Network
Kosten

Project management (KKS Innsbruck): 74.000 €
Statistics (Department of Biostatistics Innsbruck): 13.200 €
Labelling (Pharmacy Salzburg): 4.000 €
IMP Shipment (Salzburg): 2.000 €
CRF-Print: 4.000 €
Travel Costs: 10.000 €
Monitoring and Pharmacovigilance: 108.000 €
Employment of 2 labors: 172.000 €
Total: 497.200 €

Actual Funding:
LFB – unrestricted grant: 100.000 €
Coalition Warfare Grant/US Army 207.000 €
University Innsbruck: 200.000 €
Total: 507.000 €
The Cologne protocol

1. Einschluss

✓ Stumpfes Trauma (überlebbarl)
✓ > 18 Jahre
✓ V.a. Blutung
  Sichtbare Blutung, Blut auf Boden
  Umfangzunahme Bauch und Oberschenkel
  Thorax / Becken instabil
✓ Schock (RR ↓, Volumenbedarf ↑)
✓ Zielklinik Merheim

2. Blutabnahmen vor Gabe!

1x EDTA  3x Citrat  1x BGA
2,7 ml  2 x 3 ml und 1 x 10 ml  2 ml

3. Dosierung (1 Flasche über 5 min iv)

KG < 90 kg 3 Flaschen (15 min)
KG > 90 kg 4 Flaschen (20 min)

Ausschluss Isoliertes SHT
T < 30°C Schwangerschaft
<table>
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<th>ZEITPUNKT</th>
<th>T1 am Ort</th>
<th>T2 ER</th>
<th>T3 3h</th>
<th>T4 9h</th>
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**Ausbereitung Citratplasma:** Zentrifugation (5000g) für 15min; 4 Aliquote je 500μl Citrat-Plasma (3,2%) in 1,8ml Rübs und bei -70 (±10) °C einfrieren!

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... Thank you for your attention ...