Fibrinogen Concentrate and Viscoelastic Testing – Targeting the Essence of Trauma Coagulopathy, or an Unholy Alliance?

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Colonel, Joint Health Command, Australian Defence Force
Director of Clinical Services, 2nd General Health Battalion, Australian Army
Disclosures

Financial conflicts of interest: None
Funding acknowledgments:

Academic interest:
Bottom line

• I believe fibrinogen replacement is important in major bleeding

• I believe guiding fibrinogen replacement with TEG or ROTEM is likely to be better than guessing the appropriate dose
Fibrinogen is required to make strong clot
Fibrinogen is readily diluted

Hemostatic Factors and Replacement of Major Blood Loss with Plasma-Poor Red Cell Concentrates (Anesth Analg 1995;81:360–5)

Seppo T. Hiippala, MD, Gunnar J. Myllylä, MD, and Elina M. Vahtera, PhD

Table 1. Critical Level of Hemostatic Factors and the Inversely Predicted Corresponding Blood Loss (95% Confidence Interval) as Percent of Calculated Blood Volume

<table>
<thead>
<tr>
<th>Hemostatic factor</th>
<th>Critical level</th>
<th>Blood loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>$50 \times 10^3$/mm$^3$</td>
<td>230 (169–294)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.0 g/L</td>
<td>142 (117–169)</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>20</td>
<td>201 (160–244)</td>
</tr>
<tr>
<td>Factor V</td>
<td>25</td>
<td>229 (167–300)</td>
</tr>
<tr>
<td>Factor VII</td>
<td>20</td>
<td>236 (198–277)</td>
</tr>
</tbody>
</table>

The first factor that would fall to a ‘critical’ level
Low fibrinogen and coagulopathy are associated with worse outcome

Prevalence, predictors and outcome of hypofibrinogenemia in trauma: a multicentre observational study

Jostein S Hagen1,2, Simon Stanworth3, Nicole P Juffermans4,5, Karin Brohi6, Mitchell Jay Cohen7, Par I Johansson8, Jo Reikli9,10, Torsten Ellen1, Paal A Naess11 and Christine Gaarder12

1,133 patients

Fibrinogen concentration on arrival below an estimated threshold value of 2.29 g/l is strongly related to poor outcome.

For the piecewise linear model, the breakpoint (95% confidence interval (CI)) is estimated at 229 (193, 264).

piecewise linear model for relationship between fibrinogen concentration and 28-day survival.
There is a problem .. We have a solution!
But not really …

Fibrinogen Concentrate Approval Under National Blood Arrangements

Under NBA arrangements Fibrinogen Concentrate will be available only on a managed basis for the following restricted purpose:

a) For treatment of acute bleeding (including prophylaxis for high risk patients) in patients with congenital fibrinogen deficiency (including afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia); and

b) In accordance with management arrangements and oversight by a recognised Haemophilia Treatment Centre

Fibrinogen Concentrate became available under NBA arrangements from 1 July 2014 and will be held at Haemophilia Treatment Centres (HTC), with HTC Director authorisation required for access.
Why not!

Association ≠ causation

Greater severity of injury

Coagulopathic

More likely to die

Further: fixing coagulopathy does not necessarily affect mortality

Association ≠ causation
Clinical and mechanistic drivers of acute traumatic coagulopathy

Mitchell Jay Cohen, MD, Matt Kutcher, MD, Britt Redick, BA, Mary Nelson, RN, MPS, Muriah Call, BS, M. Margaret Knudson, MD, Martin A. Schreiber, MD, Eileen M. Bulger, MD, Peter Muskat, MD, Louis H. Alarcon, MD, John G. Myers, MD, Mohammad H. Rahbar, PhD, Karen J. Brasel, MD, MPH, Herb A. Phekan, MD, MSCS, Deborah J. del Junco, PhD, Erin E. Fox, PhD, Charles E. Wade, PhD, John B. Holcomb, MD, Bryan A. Cotton, MD, and Nena Matijevic, PhD, on behalf of the PROMMTT Study Group, San Francisco, California

Why not!

### TABLE 4. Factor Levels by INR and PTT-Based Coagulopathy

<table>
<thead>
<tr>
<th>INR-Based</th>
<th>Coagulopathic (n = 69)</th>
<th>Noncoagulopathic (n = 87)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrinogen</strong></td>
<td>279 ± 34</td>
<td>209 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Factor II</strong></td>
<td>61.9 ± 24.0</td>
<td>74.5 ± 26.1</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Factor V</strong></td>
<td>35.1 ± 23.0</td>
<td>57.6 ± 30.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Factor VII</strong></td>
<td>74.0 ± 29.9</td>
<td>91.5 ± 37.6</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Factor VIII</strong></td>
<td>302.0 ± 237.4</td>
<td>405.6 ± 237.4</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Factor IX</strong></td>
<td>108.4 ± 78.1</td>
<td>125.4 ± 102.2</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Factor X</strong></td>
<td>60.3 ± 25.0</td>
<td>72.5 ± 32.6</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>aPC</strong></td>
<td>37.2 (13.5–64.6)</td>
<td>8.1 (1.1–16.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Why not!

Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy


Methods: Patients undergoing elective aortic surgery requiring cardiopulmonary bypass were randomly assigned to receive FCH or placebo. Study medication was administered to patients with a 5 min bleeding mass of 60–250 g after separation from bypass and surgical haemostasis. A standardized algorithm for allogeneic blood product transfusion was followed if bleeding continued after study medication.


**Parameter** | **FCH (n=78)** | **Placebo (n=74)** | **P-value**
--- | --- | --- | ---
**Primary end point**
Total number of units of allogeneic blood product during first 24 h after study medication | 5.0 (2.0–11.0) | 3.0 (0.0–7.0) | 0.026
Median (IQR) | | | |
Units of FFP administered (first 24 h) | 4.0 (0.0–6.0) | 0.0 (0.0–4.0) | 0.017
Median (IQR) | | | |
Units of platelet concentrate administered (first 24 h) | 1.0 (0.0–2.0) | 1.0 (0.0–1.0) | 0.089
Median (IQR) | | | |

Higher fibrinogen INCREASED blood product requirement!
Cryoprecipitate or FFP are alternatives??

Fibrinogen concentrate 1g
$785.83
20g/L

FFP
$185.96 - $278.54 / unit
2g/L

Cryoprecipitate
$165.05--$346.33 / unit
8-16g/L

Cost of European Guideline empiric therapeutic dose (4g or 20 single-donor units):
$3143.32
av. $1161.25 (but req. 2L volume)
$3301
Cryoprecipitate or FFP are alternatives??

FFP and cryoprecipitate transfusions are delayed, which (at least in part) contributed to ratios far from 1:1
Cryoprecipitate or FFP are alternatives??

Trauma Massive Transfusion Registry patients:
- 75% received fibrinogen (mostly Cryo)
- Median total estimated dose: 4g (IQR 2.5-7)
- Median time for laboratory to issue cryo 1.5 hr (IQR 0.8-3.3hr)

Fibrinogen administration using cryoprecipitate is SLOW
SO: Fibrinogen concentrate …

- Widespread use in northern Europe
- ‘Expensive’ (A$785 per gram)
- Virally inactivated – but sourced from many donors, and unidentified infectious agents might be a remote possibility
- Quicker to give
- Temperature stable
- Known dose – but optimal dose unknown
- Unlike FFP, does not replace volume lost with colloid
SO: Fibrinogen concentrate …
The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition

Rolf Rossaint¹, Bertil Bouillon², Vladimir Cerm³,⁴,⁵, Timothy J. Coats⁶, Jacques Duranteau⁷, Enrique Fernández-Mondéjar⁸, Daniela Filippescu⁹, Beverley J. Hunt¹₀, Radko Komadina¹₁, Giuseppe Nardi¹², Edmund A. M. Neugebauer¹³, Yves Ozier¹⁴, Louis Riddez¹⁵, Arthur Schultz¹⁶, Jean-Louis Vincent¹⁷ and Donat R. Spahni¹⁸

**Recommendation 27** If a plasma-based coagulation resuscitation strategy is used, we recommend that plasma (FFP or pathogen-inactivated plasma) be administered to maintain PT and APTT <1.5 times the normal control. (Grade 1C)

We recommend that plasma transfusion be avoided in patients without substantial bleeding. (Grade 1B)

**Recommendation 28** If a concentrate-based strategy is used, we recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5–2.0 g/l. (Grade 1C)

We suggest an initial fibrinogen supplementation of 3–4 g. This is equivalent to 15–20 single donor units of cryoprecipitate or 3–4 g fibrinogen concentrate. Repeat doses must be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels. (Grade 2C)
Systematic review of fibrinogen in trauma coagulopathy

Efficacy and safety of fibrinogen concentrate in trauma patients—a systematic review

C. Aubron, MD, PhD, a, b, M.G. Readle, MBBS, MPH, DPhil, FANZCA, FCICM, b, J.F. Fraser, MBCHB, PhD, MRCP, FRCA, FFARCSI, FCICM b; D.J. Cooper, BMBS, MD, FRACP, FCICM a

Journal of Critical Care xxx (2014)

No RCTs found in trauma patients

Results: The systematic review identified 12 articles reporting FC usage in trauma patients: 4 case reports, 7 retrospective studies, and 1 prospective observational study. Three of these were not restricted to trauma patients.

Conclusions: Despite methodological flaws, some of the available studies suggested that FC administration may be associated with a reduced blood product requirement. Randomized trials are warranted to determine whether FC improves outcomes in prehospital management of trauma patients or whether FC is superior to another source of fibrinogen in early hospital management of trauma patients.
Systematic review of fibrinogen in bleeding patients (in general)

Fibrinogen concentrate in bleeding patients (Review)

Wikkelsø A, Lunde J, Johansen M, Stenshale J, Wetterslev J, Møller AM, Afshari A

Authors’ conclusions

In the six available RCTs of elective surgery, fibrinogen concentrate appears to reduce transfusion requirements, but the included trials are of low quality with high risk of bias and are underpowered to detect mortality, benefit or harm. Furthermore, data on mortality are lacking, heterogeneity is high and acute or severe bleeding in a non-elective surgical setting remains unexplored. Currently, weak evidence supports the use of fibrinogen concentrate in bleeding patients, as tested here in primarily elective cardiac surgery. More research is urgently needed.
Systematic review of fibrinogen in bleeding patients (in general)

Management of bleeding and coagulopathy following major trauma: an updated European guideline

Donat R Spahn¹, Bertil Bouillon², Vladimir Cerry³,⁴, Timothy J Coats⁵, Jacques Duranteau⁶, Enrique Fernández-Mondéjar⁷, Daniela Filipescu⁸, Beverley J Hunt⁹, Radko Komadina¹⁰, Giuseppe Nardi¹¹, Edmund Neugebauer¹², Yves Ozie¹³, Louis Ridde³¹⁴, Arthur Schultz¹⁵, Jean-Louis Vincent¹⁶ and Rolf Rossaint¹⁷

Well-designed prospective, randomised double-blinded studies evaluating the effect of fibrinogen supplementation are urgently needed.
Systematic review of fibrinogen in bleeding patients (in general)

Fibrinogen concentrate: clinical reality and cautious Cochrane recommendation

S. Kozek-Langenecker¹*, D. Fries², D. R. Spahn³ and K. Zacharowski⁴

Commenting upon the Cochrane review, argued:
• Existing blood products are not supported by trial evidence, so requiring this for fibrinogen concentrate is inappropriate
• Fibrinogen concentrate is extensively used in certain countries without apparent adverse effect
• “There are no suitable alternative treatments”
• The speed of administration of FC is substantially quicker
• Cost is different in different markets

In conclusion, we feel that the Cochrane review contains information that may mislead readers.
Systematic review of fibrinogen in bleeding patients (in general)

Fibrinogen concentrate: clinical reality and cautious Cochrane recommendation

S. Kozek-Langenecker1, D. Fries2, D. R. Spahn3 and K. Zacharowski4

S.K.-L. has received payments and travel funding from Baxter, Biotest, CSL Behring, Novo Nordisk, Octapharma, and TEM International. D.F. has received study funding, payments, and travel funding from Austrian National Bank, AOP Orphan, Astra Zeneca, Baxter, B. Braun, Biotest, CSL Behring, Fresenius Kabi, Glaxo, Haemoscope, Hemogem, Lilly, LFB, Mitsubishi Pharma, Novo Nordisk, Octapharma, and TEM International. D.R.S. has received study funding from CSL Behring, Vifor SA, Villars-sur-Glâne, and payments and travel funding from Abbott, Bocar, Aes AstraZeneca, Baxter, B. Braun, Boehringer Ingelheim, Bristol-Myers-Squibb, CSL Behring, Curascope, Ethicon Biosurgery, Fresenius, Galenica, GlaxoSmithKline, Janssen-Cilag, Beersse, Merck Sharp & Dohme, Novo Nordisk, Octapharma, Oxygen Biotherapeutics, TEM International, Ratiopharm, Roche Pharma, Schering-Plough, and Vifor Pharma. K.Z. has received payments and travel funding from CSL Behring.
Systematic review of fibrinogen in bleeding patients (in general)

A scientific journals’ duty of neutrality

B. von Bormann¹,², S. Suksompong¹, W. Schleinzer², and R. Zander³

The authors in question² - all - correctly disclosed their conflicts of interest. The liberal use of fibrinogen concentrate (FBC) in settings without proven benefit has been repeatedly promoted by them and affiliated groups,³⁴ and we are worried therapists may feel pressurised that way. We believe that the frequent and increasing application of FBC all over the world and its impressive sales figures are the consequence of ‘scientific marketing’ rather than scientific evidence.
Systematic review of fibrinogen in bleeding patients (in general)

Reply from the authors

Response to von Bormann and colleagues

S. Kozek-Langenecker

Our editorial was addressing the recommendation that the usage of FC should be confined to a controlled clinical setting or trial, a recommendation which in fact may cause harm in the absence of a suitable recommendation for an alternative treatment.

Academic science is currently open to scrutiny for all types of scientific misconduct, as we are sure von Bormann is aware, after having co-authored 35 publications with Joachim Boldt up to 1990. Boldt is currently the second most prolific fabricator of data and, so far, not all of the publications that he co-authored have been investigated for fabrication of scientific data.

It is understandable that the authors of the letter are themselves exposed to different therapeutic approaches (e.g. in Thailand), assuming they are still involved in patient care.
Theoretical arguments against fibrinogen concentrate

- Procoaguopthy / thrombo-embolic disease
- Multiple donors
- Fibrinogen concentrate lacks vonWillebrand factor and other potentially important components
- Unlike plasma, does not replace volume – which presumably must be replaced with crystalloid. This might be detrimental ...
- Studies showing improved viscoelastic results with fibrinogen administration may misrepresent in vivo coagulopathy
Theoretical problems: pro-coagulopathy

High levels of fibrinogen are associated with the risk of deep venous thrombosis mainly in the elderly

A. VAN HYLCKAMA VLEIG and F. R. ROENSAAL

In total, 474 consecutive patients with a first deep venous thrombosis and 474 age- and sex-matched control subjects were included in this study.

Odds of DVT in trauma

<table>
<thead>
<tr>
<th>Dichotomization at different cut-off points*</th>
<th>All (n = 948)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(fibrinogen level in g L⁻¹)</td>
<td>(1.7–4.6)</td>
</tr>
<tr>
<td>95th percentile (4.49)</td>
<td>2.8</td>
</tr>
<tr>
<td>90th percentile (4.11)</td>
<td>2.1</td>
</tr>
<tr>
<td>75th percentile (3.62)</td>
<td>1.6</td>
</tr>
<tr>
<td>50th percentile (3.17)</td>
<td>1.4</td>
</tr>
<tr>
<td>25th percentile (2.81)</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Theoretical problems: multiple donors

Cryoprecipitate versus commercial fibrinogen concentrate in patients who occasionally require a therapeutic supply of fibrinogen: risk comparison in the case of an emerging transfusion-transmitted infection

Arturo Pereira

A probabilistic model was used to compare cryoprecipitate to viral inactivated, commercial fibrinogen concentrate to evaluate with regard to the recipient’s risk of exposure to an emergent AIDS-like epidemic. In patients who occasionally need a therapeutic dose of fibrinogen, commercial fibrinogen would be marginally safer than cryoprecipitate if the new pathogen were sensitive to inactivation. But there is a potential high risk of exposure if the emerging agent withstands inactivation. In most of the analyzed scenarios, cryoprecipitate is safer than commercial fibrinogen as long as the odds that the new agent is sensitive to inactivation are lower than 1.000 to 1.
Theoretical problems: fibrinogen concentrate lacks vonWillebrand factor in cryo, and everything else in FFP
Theoretical problems: unlike plasma, does not replace volume

FFP is better than all artificial colloids and crystalloids in preserving the endothelial glycocalyx

Evaluation of resuscitation fluids on endothelial glycocalyx, venular blood flow, and coagulation function after hemorrhagic shock in rats

Luciana N. Torres, PhD, Jill L. Sundeen, PhD, Liao Ji, MD, Michael A. Dubick, PhD, and Loo Torres Filho, MD, PhD, San Antonio, Texas

Figure 5. EC thickness in postcapillary venules from cremaster preparations. See Figure 3 for definitions, number of animals,
Theoretical problems: viscoelastic results may misrepresent in vivo coagulopathy

Is viscoelastic coagulation monitoring with ROTEM or TEG validated?

Cristina Solomon\textsuperscript{a}, Lars M. Asmis\textsuperscript{b} and Donat R. Spahn\textsuperscript{c}

\textsuperscript{a}Department of Anesthesiology, Perioperative Care and General Intensive Care, Paracelsus Medical University, Salzburg University Hospital, Salzburg, Austria; Ludwig Boltzmann Institute for Experimental and Clinical Traumatology and AUVA Research Centre, Vienna, Austria, and CSL Behring, Marburg, Germany; \textsuperscript{b}Coagulation Lab and Centre for Perioperative Thrombosis and Hemostasis, Unilabs, Zurich, Switzerland; \textsuperscript{c}Institute of Anesthesiology, University and University Hospital of Zurich, Zurich, Switzerland

What is meant by ‘validation’?

‘Assay validation’ implies documented control of the test performance according to predefined criteria, relating for example to precision, linearity, accuracy, robustness, measurement limits. Such validation \textit{per se} does not improve the assay quality, it simply attests the ‘quality check status’ (i.e. the assay has been quality checked). ‘Clinical validation’ of an assay is different, because it requires the assessment of relevance to clinical practice.
Theoretical problems: viscoelastic results may misrepresent in vivo coagulopathy
Theoretical problems: this is potentially about to get much more common!

Figure 1. ROTEM Sigma
Reproduced with the permission of Haemoview Diagnostics, Australia.

Figure 2. TEG 6S
Reproduced with the permission of Haemonetics ANZ.
Theoretical problems

- Awarded Medal of Honour for actions in Cuban War
- Established National Parks & US Forest Service
- Ended Railroad monopoly
- Ended 1902 Coal Strike by both threatening strike-breaking using US Army and making employers agree to workers’ demands
- Funded Panama Canal

“Behind the ostensible government sits enthroned an invisible government owing no allegiance and acknowledging no responsibility to the people. To destroy this invisible government, to befoul the unholy alliance between corrupt business and corrupt politics is the first task of the statesmanship of the day.”

~President Theodore Roosevelt
Theoretical problems

Why MIGHT this be true??

• TEG / ROTEM DO seem to reduce transfusion requirements* in cardiac surgery
• *with the exception of an increase in fibrinogen (concentrate / cryoprecipitate) use
• Could fibrinogen use be increasing because we are treating the test, not the patient?
• Transfusion requirement is associated with adverse outcomes in other contexts
• However, there seems NO IMPROVEMENT in these other outcomes when TEG / ROTEM are used
• Perhaps there is a detrimental effect offsetting the positive effect?
## The only way to sort this out: clinical trials

<table>
<thead>
<tr>
<th>Trials completed</th>
<th>UK (Curry, Stanworth, Brohi) E-Fit 1</th>
<th>Canada (Callum et al) - FiIRST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Adult trauma patients&lt;br&gt;Active bleeding with shock&lt;br&gt;Activation of MTP and/or transfusion emergency (Group O) RBC</td>
<td>Injured patient at risk of bleeding:&lt;br&gt;SBP &lt;100mmHg at any time from injury until 30 min post admission AND RBC transfusion ordered</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>6g Fg Concentrate within 45min – vs. placebo</td>
<td>6g Fg Concentrate within 60 min vs. placebo</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Prepared study packs in ED.&lt;br&gt;Empty blinded bottles – use black syringe</td>
<td>FgC prepared in blood bank</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Only 69% received study intervention within 45min. Protocol declared not feasible.</td>
<td>Feasibility (96% received in &lt;1hr); FC concentration achieved was higher than placebo</td>
</tr>
<tr>
<td><strong>Progress</strong></td>
<td>Completed recruitment 48 patients</td>
<td>Completed recruitment 50 patients</td>
</tr>
</tbody>
</table>
The only way to sort this out: clinical trials

<table>
<thead>
<tr>
<th>Trials completed</th>
<th>UK (Curry, Stanworth, Brohi) CRYOSTAT-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Adult trauma patients</td>
</tr>
<tr>
<td></td>
<td>Active bleeding with shock</td>
</tr>
<tr>
<td></td>
<td>Activation of MTP and/or transfusion</td>
</tr>
<tr>
<td></td>
<td>emergency (Group O) RBC</td>
</tr>
<tr>
<td></td>
<td>&lt;3hrs from injury</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>2 pools of cryoprecipitate within</td>
</tr>
<tr>
<td></td>
<td>90min – vs. standard care</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Unblinded</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Feasibility</td>
</tr>
<tr>
<td><strong>Progress</strong></td>
<td>Completed recruitment 43 patients.</td>
</tr>
<tr>
<td></td>
<td>85% received cryo. within 90 minutes.</td>
</tr>
<tr>
<td></td>
<td>Cryo. concentration achieved was higher</td>
</tr>
<tr>
<td></td>
<td>in the cryo. Group. Trend to reduced</td>
</tr>
<tr>
<td></td>
<td>mortality (10 vs 27%, p=0.14)</td>
</tr>
</tbody>
</table>
The only way to sort this out: clinical trials

<table>
<thead>
<tr>
<th>Trials completed</th>
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<tr>
<td></td>
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<tr>
<td><strong>Inclusion</strong></td>
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<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td><strong>Progress</strong></td>
</tr>
</tbody>
</table>
The only way to sort this out: clinical trials

<table>
<thead>
<tr>
<th>Trials underway</th>
<th>UK (Davenport, Stanworth) CRYOSTAT - 2</th>
<th>Canada (Callum et al): follow-up to FiRST??</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion</td>
<td>Adult trauma patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MTP activated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Has received at least one unit of a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>blood component</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRYOSTAT-2</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Early 3 pools (15U)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cryoprecipitate(approx. 6g fibrinogen)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(within 90 min) vs. standard</td>
<td></td>
</tr>
<tr>
<td></td>
<td>transfusion therapy (i.e. MTP with no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cryo.)</td>
<td></td>
</tr>
<tr>
<td>Blinding</td>
<td>Not blinded</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>28 day mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 month functional outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90% power to detect 7% reduction in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mortality from baseline of 26%</td>
<td></td>
</tr>
<tr>
<td>Progress</td>
<td>1568 pts; commenced enrolment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>JUL17. 258 recruited to date (SEP18)</td>
<td></td>
</tr>
</tbody>
</table>
## The only way to sort this out: clinical trials

### Trials underway

<table>
<thead>
<tr>
<th></th>
<th>Austria (Fries et al): FI in TIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Adult trauma patients with “significant signs of internal bleeding” prehospital</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Approx. 50mg/kg fibrinogen concentrate or placebo</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Double-blind</td>
</tr>
</tbody>
</table>
| **Outcome**              | Primary outcome - FIBTEM MCF  
Secondary outcomes - are transfusion requirement/blood loss, thromboembolic complications, and clinical end points such as morbidity and length of stays on intensive care units and overall in the hospital |
| **Progress**             | 67 patients randomised; completed Dec 2015. Not yet presented or published |
The only way to sort this out: clinical trials

Trials underway

Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy (iTACTIC)

**PRIMARY OBJECTIVE:** compare the haemostatic effect of VHA guided transfusion strategy versus optimized non-VHA guided transfusion strategy in haemorrhaging trauma patients.

**SECONDARY OBJECTIVES:** to determine the effects of VHA-led versus optimized non-VHA guided resuscitation on organ failure, hospital stay, critical care stay, health care resource needs and mortality.

The Royal London Hospital recruited the final patient into the iTACTIC study on July 2nd.
Fibrinogen Early In Severe Trauma study (FEISTY) pilot trial

- Queensland, Australia 40-hospital pilot trial
- Inclusion: major trauma, FIBTEM A5<10mm
- Fibrinogen concentrate vs. cryoprecipitate, with doses determined by FIBTEM A5
- Outcomes: feasibility, speed of administration, fibrinogen concentration

Endorsed by ANZICS CTG March 2016

Target 100 patients enrolment completed March 2018

Courtesy Dr James Winearls, Gold Coast Hospital Australia
Fibrinogen Early In Severe Trauma study (FEISTY)

Courtesy Dr James Winearls, Gold Coast Hospital Australia
Fibrinogen Early In Severe Trauma study (FEISTY)

Courtesey Dr James Winearls, Gold Coast Hospital Australia
Fibrinogen Early In Severe Trauma study (FEISTY)

Primary outcome:
FC  29 minutes (23-40)
Cryo 60 minutes (40-80)

Kaplan-Meier estimates with 95% CI

Proportion with treatment commenced
0 0.25 0.5 0.75 1

Await Rx
Time to commence first treatment (min)

FC 35 16 3 2 1 0 0
Cryo 25 25 14 4 3 2 0

Courtesy Dr James Winearls, Gold Coast Hospital Australia
Fibrinogen Early In Severe Trauma study (FEISTY)

Secondary outcomes:
• No difference in PRBC transfused prehospital, at 24hr, or total
• Higher mortality in FC group (12 vs 3 patients); likely a spurious result

Courtesy Dr James Winearls, Gold Coast Hospital Australia
# Fibrinogen Early In Severe Trauma study (FEISTY)

## FEISTY-II (Winearls et al.)

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Adults, ABC score &gt;=2 OR “significant haemorrhage”, activation of MTP, FIBTEM A5 &lt;=10mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>3-6g fibrinogen concentrate (as determined by the FIBTEM A5) vs. 10-20U cryoprecipitate (as determined by the FIBTEM A5)</td>
</tr>
<tr>
<td>Blinding</td>
<td>Unblinded</td>
</tr>
<tr>
<td>Outcome</td>
<td>Still under discussion. ? NON-INFERIORITY IN: PRBC (units) in 1st 24hr Functional outcome at 6 months</td>
</tr>
<tr>
<td>Progress</td>
<td>Would require 2000 patients for 1U PRBC non-inferiority In-principle provision of FC by CSL-Behring agreed Seeking funding from NHMRC etc. in a 2-stage process</td>
</tr>
</tbody>
</table>

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**Courtesy Dr James Winearls, Gold Coast Hospital Australia**
Fibrinogen Early In Severe Trauma study (FEISTY)

Why this design?

1. Avoids giving FC or cryoprecipitate to patients who do not need it
2. Uses an outcome with economic relevance
3. Avoids seeking differences in mortality in a population likely to have a low preventable death rate
4. Asks the most relevant question to clinicians & blood policy-makers in Australia (&?worldwide) i.e. is the increasing use of FC, driven by the increasing use of ROTEM/TEG, an “unholy alliance” or something that at least is not inferior (in both clinical outcomes and resource utilisation) to standard care.

Courtesy Dr James Winearls, Gold Coast Hospital Australia
The Defence Chair of Military Medicine and Surgery: 
a collaboration between the Australian Defence Force and The University of Queensland

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