Current best practice and likely future innovations in blood products for trauma care

Colonel Michael Reade
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Defence Professor of Military Medicine & Surgery
University of Queensland & Australian Defence Force
Director of Clinical Services, 2nd General Health Battalion, Australian Army
Military trauma transfusion requirements

The UK military found (2008-11):

- 25-35% of military trauma patients required transfusion.
- Of these, approximately 40 - 60% required a massive transfusion.
- Quantity transfused varied by injury severity:
  - ISS > 15: 10 to 16 units (median) of red cells
  - ISS 9-15: 4 to 7 units of red cells
  - ISS 1-8: 3 to 4 units of red cells.

Civilian trauma transfusion requirements

• 10-15% of all PRBC units are used for trauma patients

• Only 8% of acute trauma patients required PRBC transfusion. These patients had a mortality of 27%

• Only 3% of acute trauma patients required >10 units in 24hrs. These patients had a mortality of 39%

Como et al., 2004
Conventional fractionated blood components - current best practice
Conventional blood components

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma: The PROPRPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baranuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Bresal, MD; MPH; Eileen M. Bulger, MD; Rachel A. Callcott, MD; MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD; MPH; Timothy C. Fabian, MD; Kenji Haba, MD; Jeffrey D. Kerby, MD; PhD; Peter Muddat, MD; Terence O’Keefe, MRCVS; MSPH; Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scala, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weinberg, MD; Jeannine L. Callum, MD; John R. Heest, MD; MPH; Nana Matjajcic, PhD; Christopher N. Miller, MD; Jean-Francois Petter, MD; David B. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPRPR Study Group

CONCLUSIONS AND RELEVANCE Among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours. Even though there was an increased use of plasma and platelets transfused in the 1:1:1 group, no other safety differences were identified between the 2 groups.
Conventional blood components

Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage

Sirat Khan, MD, Karim Brohi, MD, Manik Chana, MD, Imran Raza, MD, Simon Stanworth, MD, Christine Gaarder, MD, PhD, Ross Davenport, MD, PhD,
on behalf of the International Trauma Research Network (ITRN), London, United Kingdom

This is a prospective cohort study of ROTEM and lactate measurements taken from trauma patients recruited to the multicenter Activation of Coagulation and Inflammation in Trauma (ACTIT) study. A blood sample is taken on arrival and during the acute bleeding phase after administration of every 4 U of packed red blood cells (PRBCs), up to 12 U. The quantity of blood products administered within each interval is recorded.

Trauma Acute Care Surg. 2014;76: 561–568.

C, Patients receiving 12 U or more PRBCs.
Conventional blood components

Acute traumatic coagulopathy

Deactivates Va and VIIIa

aPC

Consumes Plasminogen Activator Inhibitor 1 (PAI-1)

Plasminogen

Plasmin

Fibrin

tPA

tPA less inhibited

Protein C

Thrombin

TxA

LYSIS

Plasmin

aPC

tPA

Thrombin

Fibrin

TxA

Plasmin

aPC

tPA

Thrombin

Fibrin

TxA

Plasmin

aPC

tPA

Thrombin

Fibrin

TxA

Plasmin
Conventional blood components

Maintaining 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, Lisa J. MD, Michael A. Dubick, PhD, and Ivo Torres Filho, MD, PhD, San Antonio, Texas

Figure 5. EG thickness in postcapillary venules from cremaster preparations. See Figure 3 for definitions, number of animals,
Conventional blood components

Platelet transfusion effects on aPC

Effect of platelets on aPC anticoagulant activity:

Inhibition of Activated Protein C by Platelets
S. M. Jane, C. A. Mitchell, L. Hau, and H. H. Salem
Department of Medicine, Monash Medical School, Prahran, Victoria, Australia
Conventional blood components: controversies

Relevance of the age of PRBCs?

Age of Transfused Blood in Critically Ill Adults

The ABLE Investigators and the Canadian Critical Care Trials Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fresh Blood</th>
<th>Standard Blood</th>
<th>Absolute Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome, death by day 90</td>
<td>449/1211 (37.0%)</td>
<td>430/1219 (35.3%)</td>
<td>1.7 (-2.1 to 5.5)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ICU</td>
<td>324/1214 (26.7%)</td>
<td>295/1217 (24.2%)</td>
<td>2.5 (-1.0 to 5.9)</td>
</tr>
<tr>
<td>In hospital</td>
<td>403/1212 (33.3%)</td>
<td>386/1211 (31.9%)</td>
<td>1.4 (-2.3 to 5.1)</td>
</tr>
<tr>
<td>By day 28</td>
<td>371/1212 (30.6%)</td>
<td>355/1225 (28.8%)</td>
<td>1.7 (-1.9 to 5.4)</td>
</tr>
<tr>
<td>Major illnesses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple organ dysfunction syndrome</td>
<td>162/1208 (13.4%)</td>
<td>157/1207 (13.0%)</td>
<td>0.4 (-2.8 to 3.1)</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>69/1208 (5.7%)</td>
<td>80/1207 (6.6%)</td>
<td>-0.9 (-2.8 to 1.0)</td>
</tr>
<tr>
<td>Cardiovascular failure</td>
<td>61/1206 (5.1%)</td>
<td>51/1207 (4.2%)</td>
<td>0.8 (-0.8 to 2.5)</td>
</tr>
<tr>
<td>Cardiac ischemia or infarction</td>
<td>54/1206 (4.5%)</td>
<td>46/1207 (3.8%)</td>
<td>0.8 (-0.7 to 2.4)</td>
</tr>
<tr>
<td>Deep-vein thrombosis or pulmonary embolism</td>
<td>43/1206 (3.6%)</td>
<td>43/1207 (3.6%)</td>
<td>0.0 (-1.5 to 1.5)</td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>411/1206 (34.1%)</td>
<td>378/1207 (31.3%)</td>
<td>2.8 (-0.9 to 6.5)</td>
</tr>
<tr>
<td>Acute transfusion reaction</td>
<td>4/1206 (0.3%)</td>
<td>6/1207 (0.5%)</td>
<td>-0.2 (-0.7 to 0.3)</td>
</tr>
</tbody>
</table>
Conventional blood components: controversies

Relevance of the age of PRBCs?

STandaRd Issue TrANsfusion versus Fresher red blood cell Use in intenSive carE – a randomised controlled trial.

Hypothesis

In critically ill patients who require a RBC transfusion, compared to standard practice, the administration of the freshest available compatible RBC reduces 90-day patient mortality.
Conventional blood components: controversies

Is group A thawed plasma suitable as the first option for emergency release transfusion?

\[ \text{TRANSFUSION 2014;54:1751-1755.} \]

Vishesh Chhibber,1,2,4,5 Mindy Greene,6 Michelle Vauthrin,7 Jeff Bailey,1,2,4,5 and Robert Weinstein1,2,4,5

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No hemolytic transfusion reactions or other adverse events related to transfusion were seen in any of these 23 patients.

Emergency Release Requests for Plasma: 385

- Group A or O: 325
  - Compatible thawed plasma available: 26
    - Incompatible Group A plasma transfused: 23
    - Plasma requested but not transfused: 5
  - Expiration before blood group determined: 6
- Group B or AB: 54

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Gp A rather than AB plasma as a universal donor?
Conventional blood components: controversies

Utility of TEG / ROTEM

Haemotherapy algorithm for the management of trauma-induced coagulopathy: an Australian perspective

- The trauma MHP is a controversial and fiercely debated topic.
- Three common strategies—fixed ratio MHP, VHA-guided MHP and hybrid MHP.
- High blood product ratios in FRMHP can improve outcomes.
- VHA-guided MHP may allow targeted and individualized interventions.
- Hybrid MHP strategy may combine best attributes of FRMHP and VHA guided.
- Evolving use of factor concentrates as yet unsupported by high-level evidence.
Conventional blood components: controversies

Utility of TEG / ROTEM

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

ClinicalTrials.gov Identifier: NCT020593877

Verified October 2015 by Queen Mary University of London

Sponsor:
Queen Mary University of London

Collaborators:
Oslo University Hospital
Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)
Klinikum der Universität Köln
Rigshospitalet, Denmark
Oxford University Hospitals NHS Trust
Barts & The London NHS Trust
European Commission

Currently recruiting

392 patients
Current best practice

• Aim for 1:1:1 \( (\frac{1}{5}) \)

• Use a Massive Transfusion Protocol

• Expect to replace fibrinogen in addition to plasma

• (Possibly) use a TEG / ROTEM to avoid unnecessary products transfused
Likely future innovations
Likely future innovations:
Whole blood
Historical use: stored & fresh whole blood

- WWII (UK military): 3 million units stored WB
- WWII (US military): Initially used only blood substitutes (FDP & albumin); by last year of war, 500,000 units stored WB prepared in 13 months
- Vietnam War (US military): 600,000 units stored WB transfused
- Iraq / Afghanistan: 10,000 units FWB transfused vs. 153,000 units PRBC transfused

i.e. the ABCA military has (mostly) moved from *stored* WB by preference to FWB if nothing else is available
Walking Donors (fresh whole blood)

FWB compared to 1:1:1:

• Advantages:
  • Less anticoagulant / additive
  • Hct 38% vs. <30%
  • Coagulation factors 83% vs. 50% of circulating blood in health
  • Platelet count 240,000 vs. 80,000

• Disadvantages
  • Graft vs. host disease (only 1 US military fatal case reported)
  • Hepatitis C risk (1 reported case, but 3 / 2,222 donor samples positive for Hep C)
  • 1 x HTLV transmission
  • Loss of platelets if passed through a conventional white-cell filter
Coagulation function of stored whole blood is preserved for 14 days in austere conditions: A ROTEM feasibility study during a Norwegian antipiracy mission and comparison to equal ratio reconstituted blood

Geir Strandenes, MD, Ivar Austlid, MD, Torunn O. Apelseth, MD, PhD, Tor A. Hervig, MD, PhD, Jan Sommerfelt-Pettersen, MD, Maryanne C. Herzig, PhD, Andrew P. Cap, MD, PhD, Heather E. Pidcocke, MD, PhD, and Einar K. Kristoffersen, MD, PhD, Bergen, Norway
Walking Donors (fresh whole blood): observational study

Warm Fresh Whole Blood is Independently Associated With Improved Survival for Patients With Combat-Related Traumatic Injuries
Philip C. Spearman, MD, James G. Proctor, MD, Kurt R. Gurchiek, MD, and C. Bedley, MD, and Army A. Arand, MD

Results: Of 354 patients analyzed there were 100 in the WFWB and 254 in the CT group. Patients in both groups had similar severity of injury determined by admission eye, verbal, and motor Glasgow Coma Score, base deficit, international normalized ratio, hemoglobin, systolic blood pressure, and injury severity score.

FWB was associated with:
- Less total volume transfused
- (implausibly?) higher 24hr and 30-day survival

Table 6 Multivariate Logistic Regression With Treatment Groups for 30-d Survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95.0% C.I.)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFWB group</td>
<td>12.4 (1.8–80)</td>
<td>0.01</td>
</tr>
<tr>
<td>Plasma:RBC ratio</td>
<td>11.7 (2.6–52)</td>
<td>0.001</td>
</tr>
<tr>
<td>ISS</td>
<td>0.94 (0.91–0.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>GCS eyes (normal)</td>
<td>4.1 (1.5–10.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Base deficit</td>
<td>0.88 (0.82–0.95)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Stored whole blood: trial

A Randomized Controlled Pilot Trial of Modified Whole Blood versus Component Therapy in Severely Injured Patients Requiring Large Volume Transfusions

Bryan A. Cotton, MD, MPH(*) Janet P. Podbielniak, RN, BSN; Elizabeth Camp, MS, MPH; Timothy Welch, RN, MSN, RNCRNP; Deborah del Amo, MD; Jee-Hoi Wong, MD; Thomas J. Faries, MD (ASC); Rosemary A. Kasan, MD, PhD; Charles E. Wade, PhD(*) and John B. Holcomb, MD(*) on behalf of The Early Whole Blood Investigators

Single-centre RCT
WB stored up to 5 days
Passed through white cell filter that removed platelets – therefore platelets supplemented
Walking Donors (fresh whole blood)

No “universal donor” for FWB?

Current US & AS military guidelines:

Donor FWB must be an ABO type-specific match to the casualty. If not matched, a fatal hemolytic reaction may occur. TYPE O whole blood is NOT universal.

Arguments for low-titre O as a universal donor

LOW TITER GROUP O WHOLE BLOOD IN EMERGENCY SITUATIONS

Geir Strandenes,1 Ole Berséus,2 Andrew P. Cap,5 Tor Hervig,4 Michael Reade,7 Nicolas Prat,4,5 Anne Sailliol,57 Richard Gonzales,57 Clayton D. Simon,57 Paul Ness,8 Heidi A. Doughty,7 Philip C. Spinella,4,5,8, and Einar K. Kristoffersen4

Readily available due to high frequency of low-titer group O donors (approximately 95%–70% of group O donors if IgG <400, IgM <100)
Several observational studies suggest fresh whole blood is associated with better outcomes ... but residual confounding remains likely.

One underpowered clinical trial showed no benefit.

In vitro assessments of stored whole blood suggest cold storage up to 21 days preserves adequate haemostatic function.

In Western countries, the blood supply implications of providing large quantities of FWB / cold-stored WB are substantial.

We need a clinical trial that assesses:

1. Clinical effect
2. Cost effectiveness

(depending on who ‘we’ are .....)
Likely future innovations:
Factor concentrates
Fibrinogen concentrate

- FFP 2g/ L
- Cryoprecipitate 8-16g/ L
- Fibrinogen concentrate 20g/ L
Fibrinogen concentrate

Trauma Massive Transfusion Registry patients:
- 75% received Fg replacement (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
Fibrinogen concentrate: observational studies

Administration of fibrinogen concentrate in exsanguinating trauma patients is associated with improved survival at 6 hours but not at discharge.

Arausch Waafaideh, MD, Rolf Loefring, PhD, Marc Maegle, MD, Thomas Brockamp, MD, Manuel Mutschler, MD, Sven Lendemans, MD, Marc Banerjee, MD, Bernd Bouillon, MD, Christian Probst, MD, and the Trauma Registry of DGU, Cologne, Germany

Patients documented in the Trauma Registry of the German Society for Trauma Surgery (primary admissions, Injury Severity Score [ISS] ≥16) who had received FC during initial care between emergency department (ED) arrival and intensive care unit admission (FC+) were matched with patients who had not received FC (FC−).

<table>
<thead>
<tr>
<th>Fibrinogen Group (FC+)</th>
<th>Control Group (FC−)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator days, mean ± SD, d</td>
<td>12.2 ± 14.2</td>
<td>11.3 ± 14.7</td>
</tr>
<tr>
<td>ICU LOS, mean ± SD, d</td>
<td>17.2 ± 17.6</td>
<td>17.3 ± 17.9</td>
</tr>
<tr>
<td>Hospital LOS, mean ± SD, d</td>
<td>34.6 ± 33.3</td>
<td>32.8 ± 28.4</td>
</tr>
<tr>
<td>Thromboembolic event, %</td>
<td>6.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Sepsis, %</td>
<td>20.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Organ failure, %</td>
<td>73.8</td>
<td>61.9</td>
</tr>
<tr>
<td>Multiple organ failure, %</td>
<td>61.2</td>
<td>49.0</td>
</tr>
<tr>
<td>Time to death, mean ± SD, d</td>
<td>7.5 ± 14.6</td>
<td>4.7 ± 8.6</td>
</tr>
<tr>
<td>6-hour mortality, %</td>
<td>10.5</td>
<td>16.7</td>
</tr>
<tr>
<td>24-hour mortality, %</td>
<td>13.9</td>
<td>18.4</td>
</tr>
<tr>
<td>30-day mortality, %</td>
<td>27.9</td>
<td>24.8</td>
</tr>
<tr>
<td>In-hospital mortality overall, %</td>
<td>28.6</td>
<td>25.5</td>
</tr>
</tbody>
</table>

FC:
- Lower 6 hour mortality
- Delayed death
- Higher rates of thromboembolic events and organ failure
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.
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

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, Hemagain, 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, Baar, Amgen, AstraZeneca, Baxter, B. Braun, Boehringer Ingelheim, Bristol-Myers-Squibb, CSL Behring, Curacyte, Ethicon Biosurgery, Fresenius, Galenica, GlaxoSmithKline, Janssen-Cilag, Beerse, 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.
The authors in question – 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, 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

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 problems with fibrinogen concentrate

- Cost?
- Procoaguopathy / thrombo-embolic disease?
- Multiple donors?
- Studies showing improved viscoelastic results with fibrinogen administration may misrepresent in vivo coagulopathy.
Theoretical problems with fibrinogen concentrate: cost

To be economically competitive with cryo, FC must cost US$414/ g, (approx. A$517) or save on other patient costs (Okerberg et al., Vox Sanguinis 2016)

<table>
<thead>
<tr>
<th>Fibrinogen concentrate (plasma derived - imported)</th>
<th>RiaSTAP</th>
<th>1g</th>
<th>CSL Behring</th>
<th>$740.50</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Clinical fresh frozen plasma (FFP)</th>
<th>WB clinical FFP</th>
<th>295ml+/–10% [2]</th>
<th>Australian Red Cross Blood Service</th>
<th>$304.22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoprecipitate</td>
<td>WB cryoprecipitate</td>
<td>30–40ml [2]</td>
<td>Australian Red Cross Blood Service</td>
<td>$177.15</td>
</tr>
</tbody>
</table>
Theoretical problems with fibrinogen concentrate: pro-coagulopathy

POSTINJURY HYPERFIBRINOGENEMIA COMPROMISES EFFICACY OF HEPARIN-BASED VENOUS THROMBOEMBOLISM PROPHYLAXIS

Jeffrey N. Harr, Ernest E. Moore, Theresa L. Chin, Arsen Ghasabian, Eduardo Gonzalez, Max V. Wohlauer, Angela Sauaia, Anirban Banerjee, and Christopher C. Stillman


Methods: In vitro studies evaluated thromboelastography (TEG) parameters in 10 healthy volunteers after the addition of fibrinogen concentrate and heparin.

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 10)</th>
<th>Heparin (n = 10)</th>
<th>Fibrinogen (n = 10)</th>
<th>Heparin + fibrinogen (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R time, min</td>
<td>8.51 ± 0.69</td>
<td>15.53 ± 1.48*</td>
<td>5.93 ± 0.19*</td>
<td>9.57 ± 0.52</td>
</tr>
<tr>
<td>k Time, min</td>
<td>3.16 ± 0.3</td>
<td>6.99 ± 0.51*</td>
<td>2.22 ± 0.16*</td>
<td>4.92 ± 0.75</td>
</tr>
<tr>
<td>α Angle, degrees</td>
<td>51.74 ± 2.1</td>
<td>30.27 ± 1.78*</td>
<td>58.01 ± 2.18*</td>
<td>41.03 ± 3.14*</td>
</tr>
<tr>
<td>MA, mm</td>
<td>60.48 ± 1.43</td>
<td>52.79 ± 1.5*</td>
<td>67.53 ± 1.19*</td>
<td>61.39 ± 1.29</td>
</tr>
<tr>
<td>G, dyn/cm²</td>
<td>7.81 ± 0.45</td>
<td>5.68 ± 0.32*</td>
<td>10.58 ± 0.52*</td>
<td>8.08 ± 0.41</td>
</tr>
<tr>
<td>Thrombus generation, mm/min</td>
<td>736.2 ± 18.1</td>
<td>651.7 ± 18.4*</td>
<td>825.9 ± 14.7*</td>
<td>736.2 ± 19.2</td>
</tr>
</tbody>
</table>

The addition of fibrinogen to heparinized blood negated the anticoagulant effects of heparin.
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 with fibrinogen concentrate: effect on TEG/ROTEM might not reflect effect on clotting

- TEG / ROTEM usage combined with FC appears to reduce plasma usage
- FC might not preserve the endothelial glycocalyx as well as plasma
- TEG / ROTEM do not assess endothelial contribution to clotting

SO:
Good (avoiding transfusion) and bad (not treating the endothelial component coagulopathy) effects might be cancelling one another out
Management of bleeding and coagulopathy following major trauma: an updated European guideline


Spahn et al. Critical Care 2013, 17:R76

Well-designed prospective, randomised double-blinded studies evaluating the effect of fibrinogen supplementation are urgently needed.
Fibrinogen concentrate: trials completed

Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial

Lancet Haematol 2017; 4:e258–71

Petr Oehmichen, Dietmar Fries, Markus Mittendorf, Nicole Innerhofer, Daniel von Langeren, Tobias Helt, Gottfried Gobler, Stefan Schmied, Barbara Frisenbuecker, Ingo H Lorenz, Matthias Stohle, Verena Rastner, Susanne Treitlreiter, Helmut Raab, Benedict Tremi, Dieter Wally, Benjamin Treichl, Agnes Mays, Christof Kronerwitter, Edgar Oswald

The FFP group and 50 patients in the CFC group were included in the final interim analysis. The study was terminated early for futility and safety reasons because of the high proportion of patients in the FFP group who required rescue therapy compared with those in the CFC group (23 [52%] in the FFP group vs two [4%] in the CFC group; odds ratio [OR] 25·34 [95% CI 5·47–240·03], p<0·0001) and increased needed for massive transfusion (13 [30%] in the FFP group vs six [12%] in the CFC group; OR 3·04 [0·95–10·87], p=0·042) in the FFP group.

Planned primary outcome: multiple organ failure

Analysis excluded patients who discontinued planned treatment
Fibrinogen concentrate: trials completed

**Feasibility study**

- **Intervention - Cryo (~4g Fg) vs. standard care**
- 85% received cryo within 90min (median time 60min)
- Mean Fg concentration higher during resuscitation (2.1 vs 0.9 at 8U RBC) but no difference at 24h
- No difference in RBC transfusion & non-significant difference in mortality (10% vs 28%, p=0.14)

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*Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial*

N. Curry¹,², C. Rourke², R. Davenport², S. Beer¹, L. Pankhurst³, A. Deary³, H. Thomas³, C. Llewelyn³, L. Green⁴, H. Doughty⁶, G. Nordmann⁶, K. Brohi⁵, and S. Stanworth¹
Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial

B. Nascimento1,*, J. Callum1, H. Tien1, H. Peng2, S. Rizoli3, P. Karanicolas1, A. Alam1, W. Xiong1, R. Selby1, A-M. Garzon1, C. Colavecchia3, R. Howald1, A. Nathens1, and A. Beckett4


Methods. Fifty hypotensive (systolic arterial pressure ≤100 mm Hg) adult patients requiring blood transfusion were randomly assigned to either 6 g of FC or placebo, between Oct 2014 and Nov 2015 at a tertiary trauma centre. The primary outcome, feasibility, was assessed by the proportion of patients receiving the intervention (FC or placebo) within one h of hospital arrival. Plasma fibrinogen concentration was measured, and 28-day mortality and incidence of thromboembolic events were assessed.

Conclusions. Early infusion of FC is feasible and increases plasma fibrinogen concentration during trauma resuscitation. Larger trials are justified.
### Fibrinogen: trials underway

<table>
<thead>
<tr>
<th></th>
<th>UK (Curry, Stanworth, Brohi): Cryostat</th>
<th>Canada (Callum et al): FiiRST 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Adult trauma patients</td>
<td>Injured patient at risk of bleeding: SBP &lt;100mmHg at any time from injury until 30 min post admission AND RBC transfusion ordered</td>
</tr>
<tr>
<td></td>
<td>Active bleeding with shock</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activation of MTP and Transfusion of at least one unit of PRBC</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>15U cryoprecipitate (approx. = 6g Fg Concentrate) within 45min vs. standard care</td>
<td>6g Fg Concentrate within 60 min vs. standard care</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Prepared study packs in ED. Empty blinded bottles – use black syringe</td>
<td>FgC prepared in blood bank</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>28-day mortality</td>
<td>28-day mortality</td>
</tr>
<tr>
<td><strong>Progress</strong></td>
<td>Funded to recruit 1568 patients</td>
<td>Funded, ?? patients</td>
</tr>
</tbody>
</table>
Fibrinogen concentrate: trials underway

Strategy of Transfusion in Trauma Patients - STATA Trial

- *Verified July 2015 by University of Sao Paulo General Hospital*
- **Sponsor:** University of Sao Paulo General Hospital
- **Information provided by (Responsible Party):** University of Sao Paulo General Hospital
- **ClinicalTrials.gov Identifier:** NCT02416817
- **First received:** August 28, 2014
- **Last updated:** July 30, 2015
- **Last verified:** July 2015

Fibrinogen Concentrate (FGTW) in Trauma Patients, Presumed to Bleed (Fi in TIC)

- *Verified April 2015 by Medical University Innsbruck*
- **Sponsor:** Medical University Innsbruck
- **Information provided by (Responsible Party):** Dietmar Fries, M.D., Medical University Innsbruck
- **ClinicalTrials.gov Identifier:** NCT01475344
- **First received:** October 27, 2011
- **Last updated:** April 16, 2015
- **Last verified:** April 2015

Completed; not yet published

Completed; not yet published
Fibrinogen Early In Severe Trauma study (FEISTY)

- Queensland, Australia multicentre 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

Currently underway

Courtesy Dr James Winnearls, Gold Coast Hospital Australia
**Aims**

1. To determine feasibility of earlier Fg replacement with either FgC or cryo in trauma patients with haemorrhage
2. To compare Fg levels in trauma patients with haemorrhage who receive early Fg replacement with standard care.
3. To compare timing of administration of FgC with cryo in trauma patients with haemorrhage

**Design**

Feasibility study
Multi-centre, interventional, randomised controlled trial

**Primary outcome measures**

1. Time from randomisation to commencement of Fg replacement (either FgC or cryo)
2. Lowest Fg measured in the first 6 h from randomisation
In patients with massive bleeding due to trauma:

- Fibrinogen concentrate (as an alternative to FFP or cryoprecipitate) appears highly attractive

BUT

- The optimal dose is unclear (and so the pro-thrombotic tendency is unknown)
- There remains a requirement for volume replacement ... but with what?
- Other factors may require replacement
- There are potential safety concerns

THEREFORE: 2013 European guidelines expressing equipoise for a trial are correct.

Relevant trial programs are underway
Likely future innovations: Cryopreserved components
Cryopreserved components

PRBC

- US Dept. of Defense has 225 000 stored frozen units of PRBC
- NL military has used frozen PRBC since SFOR Bosnia 1999; >2000 units transfused in Afghanistan 2006-2011
- Stored at -65°C for 10 years
- Not routinely used in any civilian health system (yet ...)

Cryopreserved components

Transfusion of Cryopreserved Packed Red Blood Cells Is Safe and Effective After Trauma
A Prospective Randomized Trial

Martin A. Schreiber, MD,* Belinda H. McCully, PhD,* John B. Holcomb, MD,*| Bryce R. Robinson, MD,*| Joseph P. Minier, MD, MPH,* Ronald Stewart, MD,* Lucelia Kirtley, MD,*| Nicole T. Gordon, MD,*| David T. Martin, MD,* Elizabeth D. Rick, BS,* Randi K. Drain, BS,* Connor Wiley, BS,* Nathan Anderson, BA,* Denice Somoereke, MS,Ed,* Ben Houston,* Dianne Lagos, BA,* Bryan Cotton, MD,*| Tima Gomaz,* Michael W. Cripps, MD,* Mark DeRoos,* and Samantha J. Underwood, MS*

256 patients

*Ann Surg 2015;262:426-433*
Transfusion of Cryopreserved Packed Red Blood Cells Is Safe and Effective After Trauma
A Prospective Randomized Trial

Martin A. Schreiber, MD,* Belinda H. McCally, PhD,* John B. Holcomb, MD,* Bryce E. Robinson, MD,* Joseph P. Minei, MD, MPH,‡ Ronald Stewart, MD,‡ Liezel Kiraly, MD,* Nicole T. Gordon, MD,* David F. Martin, MD,* Elizabeth S. Bick, BS,§ Randi K. Deon, BS,* Connor Wiles, BS,* Nathan Anderson, BA,* Dennis Sonneroke, MS, Ed,* Ben Foster,* Diane Lopez, BA,* Bryan Cotten, MD,* Dima Gomaa,* Michael W. Cripps, MD,* Mark DelRosa,* and Samantha J. Underwood, MD*


256 patients

<table>
<thead>
<tr>
<th>TABLE 3. Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Total patients</td>
</tr>
<tr>
<td>Acute renal failure</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
</tbody>
</table>

Data are presented as percentage of occurrence. Total patients represent the number of patients in whom the outcome was measured daily until discharge from the hospital.
Cryopreserved components

Cryopreserved platelets

• 2 year storage at -80°C
• >1000 units transfused by NL military, without apparent adverse effect
• Only supported by one RCT involving 73 patients, 24 who received cryo. plts
Cryopreserved components

Transfusion: -80°C Frozen Blood Products Are Safe and Effective in Military Casualty Care

Femke Noorman1,2,*, Thijs T. C. F. van Dongen2,3,*, Marie-Christine J. Plat3, John F. Badloe1, John R. Hess3, Rigo Hoencamp3

This report describes for the first time that the combination of -80°C frozen platelets, plasma and red cells is safe and at least as effective as standard blood products in the treatment of (military) trauma casualties. Frozen blood can save the lives of casualties of armed conflict without the need for in-theatre blood collection. These results may also contribute to solutions for logistic problems in civilian blood supply in remote areas.

**Fig 2. Transfusion, injury and outcome of MT and non-MT patients, pre- and post-MTP. MT indicates massive transfusion,**
Cryopreserved components

ADF policy decisions:

• Cryo. platelets are TGA-approved for use only outside Australia.
• The CLIP trial is endorsed & registered with ABCA TTCP
Possible future developments
Possible future developments

- Mirasol UV pathogen-reduction of whole blood
- Cold-stored platelets
- Lyophilised plasma
- “Artificial” platelets
- S1P-enriched fluids
- Next-generation HBOC
Mirasol UV/riboflavin pathogen-reduction of whole blood

Mirasol System Surveillance Data on > 58,000 Transfusions
(>24,000 Platelet and >34,000 FFP transfusions)

- No reports of serious adverse events related to use of Mirasol-treated platelet and plasma products
- No cases of TRALI (transfusion-related acute lung injury) reported
- No reports of increased bleeding or increased platelet product utilization after introduction

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease/model for</th>
<th>Mirasol PRT System for Platelets and Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV: intra cellular cell-associated</td>
<td>AIDS</td>
<td>4.5±0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.9±0.2</td>
</tr>
<tr>
<td>Porcine Parvovirus</td>
<td>Parvovirus B-19</td>
<td>≥ 5.0</td>
</tr>
<tr>
<td>West Nile Virus</td>
<td>HCV</td>
<td>≥ 5.1</td>
</tr>
<tr>
<td>Babesia microti</td>
<td>Babesiosis</td>
<td>≥ 4</td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td>Chagas’ disease</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Leishmania donovani</td>
<td>Leishmaniasis</td>
<td>≥ 4</td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>Malaria</td>
<td>≥ 3.2</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>n/a</td>
<td>No regrowth</td>
</tr>
</tbody>
</table>
Cold-stored platelets

One size doesn’t fit all: Should we reconsider the introduction of cold-stored platelets in blood bank inventories? [version 1; referees: 2 approved]

Alessandra Berzuini, Marta Spreamico, Daniele Prati
Department of Transfusion Medicine and Hematology, Azienda Sussidiaria Sanitaria Terniense (ASST) di Lecce, Alessandro Manzoni Hospital, Lecce, Italy

Table 3. List of in vitro experiments comparing platelet storage at 4°C versus room temperature.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>Year</th>
<th>4°C versus room temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al.</td>
<td>Transfusion</td>
<td>2016</td>
<td>Reduced glycolysis, increased expression of P-selectin, faster thrombin generation, faster clot formation, equal strength</td>
</tr>
<tr>
<td>Byrum et al.</td>
<td>Transfusion</td>
<td>2016</td>
<td>Less oxidative stress, stronger clot, increased response to aggregating agents, better aggregation in shear stress conditions</td>
</tr>
<tr>
<td>Getz et al.</td>
<td>Transfusion</td>
<td>2016</td>
<td>No difference in platelet content in the first 5 days of storage, no difference in rotation thromboelastometry (ROTEM) pattern after 5 days of storage</td>
</tr>
<tr>
<td>Wood et al.</td>
<td>Transfusion</td>
<td>2016</td>
<td>Decreased expression of GP1B, GP1X, GP1B, and GPV (easier von Willebrand factor attack), increased expression of P-selectin, tansaparin, and phosphatidylserine, cytokine protein modifications corresponding to activation state (promenous), increased expression of CD40, CD63, and annexin V</td>
</tr>
<tr>
<td>Barmukanova et al.</td>
<td>Transfusion</td>
<td>2016</td>
<td>Increased aggregation potential</td>
</tr>
<tr>
<td>Reddick et al.</td>
<td>Shock</td>
<td>2014</td>
<td>Increased expression of CD40 and P-selectin</td>
</tr>
<tr>
<td></td>
<td>Shock</td>
<td>2016</td>
<td>Increased intracellular free calcium, increased of dense granule release of ATP, accelerated thrombin generation, more pronounced response to ADP, collagen, and TRAP (thrombin receptor-activating peptide), faster, stronger, and more durable clot</td>
</tr>
<tr>
<td>Mondoro and Vostell</td>
<td>Platelet</td>
<td>2002</td>
<td>Increased response to ADP and epinephrine, stronger clot resistance to disaggregating agents, no spontaneous aggregation</td>
</tr>
<tr>
<td>Connor et al.</td>
<td>Transfusion</td>
<td>1996</td>
<td>Reduced expression of GMP-140 in ADP response of 250%, collagen response of 100% at room temperature</td>
</tr>
<tr>
<td>Truhi et al.</td>
<td>Transfusion</td>
<td>1562</td>
<td>Increased expression of GMP-140</td>
</tr>
<tr>
<td>Rinder et al.</td>
<td>Transfusion</td>
<td>1990</td>
<td>Increased expression of GMP-140</td>
</tr>
<tr>
<td>Becker et al.</td>
<td>Transfusion</td>
<td>1989</td>
<td>More pronounced ADP response</td>
</tr>
</tbody>
</table>
Lyophilised plasma

The evolving role of lyophilized plasma in remote damage control resuscitation in the French Armed Forces Health Service

**TABLE 2. In vitro properties of FLYP compared with other French therapeutic plasmas**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>PFC-SD</th>
<th>PFC-IA</th>
<th>PFC-Se</th>
<th>FLYP</th>
<th>Physiological norms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>g/L</td>
<td>2.8</td>
<td>2.7</td>
<td>2.8</td>
<td>2.4</td>
<td>2-4</td>
</tr>
<tr>
<td>Factor V</td>
<td>IU/mL</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0-1.1</td>
<td>0.7</td>
<td>0.7-1.2</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>IU/mL</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9-1.1</td>
<td>0.7</td>
<td>0.5-1.5</td>
</tr>
<tr>
<td>Factor XI</td>
<td>IU/mL</td>
<td>0.8</td>
<td>0.6</td>
<td>0.9-1.0</td>
<td>0.7</td>
<td>0.5-1.4</td>
</tr>
<tr>
<td>Protein C</td>
<td>IU/mL</td>
<td>1.0</td>
<td>0.9</td>
<td>1.1-1.2</td>
<td>0.9</td>
<td>0.7-1.2</td>
</tr>
<tr>
<td>Protein S</td>
<td>IU/mL</td>
<td>0.6</td>
<td>1.0</td>
<td>1.3-1.4</td>
<td>0.9</td>
<td>0.7-1.4</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>IU/mL</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>α2 antiplasmin</td>
<td>IU/mL</td>
<td>0.2</td>
<td>0.8</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8-1.2</td>
</tr>
</tbody>
</table>

PFC-SD = frozen solvent-detergent plasma; PFC-IA = frozen amotosalen/UV-treated plasma; PFC-Se = frozen secured by quarantine plasma; FLYP = lyophilized amotosalen/UV-treated plasma.
"Artificial" platelets

Alternatives to allogeneic platelet transfusion

*British Journal of Haematology, 2016, 175, 381–390*

Michael J. R. Desborough,1,2 Peter A. Smethurst,2 Lisa J. Estcourt1,2 and Simon J. Stanworth1,2

<table>
<thead>
<tr>
<th>Platelet transfusion alternative</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyophilised platelets (NCT02223117)</td>
<td>Not in clinical use.</td>
</tr>
<tr>
<td>Haemostatic particles</td>
<td>Dose escalation study in healthy volunteers underway.</td>
</tr>
<tr>
<td>Liposomes</td>
<td>Animal trials only</td>
</tr>
<tr>
<td>(Hagisawa <em>et al</em> (2015))</td>
<td>Not in clinical use.</td>
</tr>
<tr>
<td>Engineered nanoparticles</td>
<td>Animal trials only</td>
</tr>
<tr>
<td>Infusible platelet membranes</td>
<td>Animal trials only</td>
</tr>
<tr>
<td>Platelets generated from stem cells</td>
<td>Limited RCT evidence in thrombocytopenic patients</td>
</tr>
<tr>
<td></td>
<td>Animal trials only</td>
</tr>
</tbody>
</table>

Joint Health Command
“Artificial” platelets

Use of fresh platelet concentrate or lyophilized platelets in thrombocytopenic dogs with clinical signs of hemorrhage: a preliminary trial in 37 dogs

Elizabeth B. Davidow, DVM, DACVECC; Benjamin Brainard, DVM, DACVA, DACVECC; Linda G. Martin, DVM, MS, DACVECC; Matthew W. Beal, DVM, DACVECC; Arthur Bode, PhD; Michael J. Ford, PhD; Noel Ramsey, BS, LVT, LATG; Alicia Fagella, DVM, DACVECC and Ari Juikowitiz, VMD, DACVECC

Animals – Thirty-seven dogs with a complaint of hemorrhage associated with thrombocytopenia (platelet count <7 x 10⁹/L [70,000/µL]), a hematocrit >15%, and that had received neither vincristine nor platelet-containing transfusions within 72 h of enrollment were studied.

Measurements and Main Results – Twenty-two dogs received LYO and 15 received FRESH. There was no difference between groups in age, weight, BLS, platelet count, white blood cell count, hematocrit, or presence of melena. There was no difference between groups in transfusion reaction rates, the need for additional transfusions, 24-h BLS, hospitalization time, survival to discharge, or 28-d survival.

Conclusions – Transfusion of LYO was feasible and associated with a low transfusion reaction rate in this limited study of thrombocytopenic canine patients presenting with mild-to-severe hemorrhage. LYO were easy to use and provided storage advantages over FRESH. Further study of this product, including examination of efficacy and platelet life span, is warranted.

Figure 1: Platelet count following platelet product administration. The line indicates no change in platelet count (x10⁹/µL) with transfusion. Dots to the left of line indicate that the platelet count increased after transfusion, dots to the right indicate that the count decreased despite transfusion. As shown, neither fresh concentrate nor lyophilized platelets were successful consistently in raising the measured count. Red, FRESH (fresh platelet concentrate); Blue, LYO (lyophilized platelets).
Exposure to a protein-poor environment causes matrix metalloproteinase (MMP) mediated syndecan-1 ectodomain shedding. Activation of the sphingosine 1-phosphate receptor inhibits the MMPs, preventing shedding, while at the same time the EG is restored by the mobilisation of intra-cellular pools of EG components via golgi-mediated translocation.

SO: resuscitation with S1P-containing fluids should be the most effective strategy
Next-generation HBOC

HBOC-201 as an Alternative to Blood Transfusion: Efficacy and Safety Evaluation in a Multicenter Phase III Trial in Elective Orthopedic Surgery
Jonathan S. Johr, MD, Colin Mackenzie, MD, L. Bruce Pearce, PhD, Arkadiy Pitsun, MS, and A. Gerson Greenburg, MD, PhD

Randomization

PRBC N = 338
100% Efficacy
No Further Treatment

HBOC-201 N = 350
Success?
No
Yes
PRBC Treatment

Conclusion: HBOC-201 eliminated transfusion in the majority of subjects. The between arms (H vs. R) safety analysis was unfavorable.

Overall comparison of treatment arms

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>0.450</th>
<th>0.016</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>H 350</td>
<td>0.03</td>
<td>2,964</td>
<td>711</td>
</tr>
<tr>
<td>R 338</td>
<td>0.02</td>
<td>334 (95)</td>
<td>273 (76)</td>
</tr>
</tbody>
</table>

Mean ± SD
The Defence Chair of Military Medicine and Surgery:

a collaboration between the Australian Defence Force and The University of Queensland

m.reade@uq.edu.au OR michael.reade@defence.gov.au