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

Colonel Michael Reade

MBBS MPH DPhil DMedSc AFRACMA FANZCA FCICM

Defence Professor of Military Medicine & Surgery
University of Queensland & Australian Defence Force
Director of Clinical Services, 2nd General Health Battalion, Australian Army

JOINT HEALTH COMMAND

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.**

Jansen et al, 2013.

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

JOINT HEALTH COMMAND

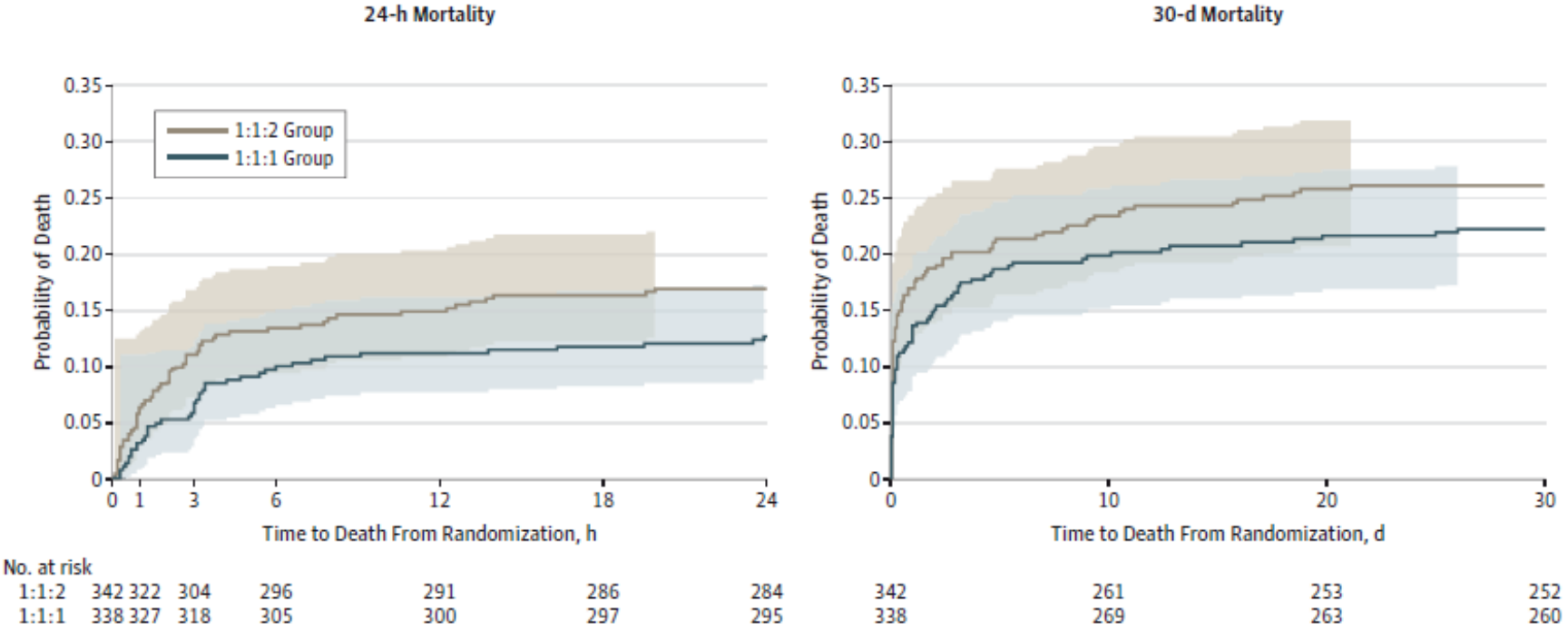
Conventional blood components

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 PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachael A. Callcut, MD, MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD, MPH; Timothy C. Fabian, MD; Kenji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Peter Muskat, MD; Terence O'Keeffe, MBChB, MSPH; Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scalea, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weinberg, MD; Jeannie L. Callum, MD; John R. Hess, MD, MPH; Nena Matijevic, PhD; Christopher N. Miller, MD; Jean-Francois Pittet, MD; David B. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

JAMA. 2015;313(5):471-482.

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.



JOINT HEALTH COMMAND

Conventional blood components

Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage

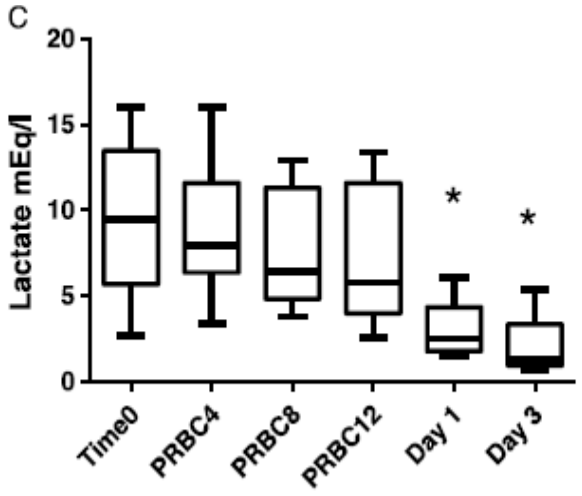
Sirat Khan, MD, Karim Brohi, MD, Manik Chana, MD, Imran Raza, MD, Simon Stanworth, MD, Christine Gaarder, MD, PhD, Ross Davenport, MD, PhD,
***on behalf of* the International Trauma Research Network (INTRN),** *London, United Kingdom*

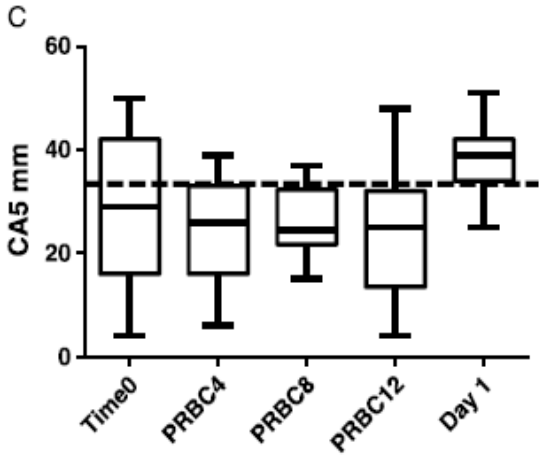
This is a prospective cohort study of ROTEM and lactate measurements taken from trauma patients recruited to the multicenter Activation of Coagulation and Inflammation in Trauma (ACIT) study. A blood sample is taken on arrival and during the acute bleeding phase after administration of every 4 U of packed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

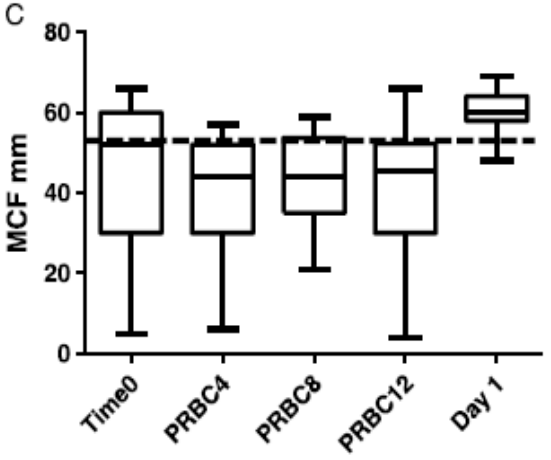
J Trauma Acute Care Surg. 2014;76: 561–568.

Transfusion of FFP/PRBC ratios greater than 1:2 throughout the bleeding episode failed to normalize any ROTEM parameters and lactic acidemia was not cleared until Day 1, after hemorrhage control had been achieved.

C, Patients receiving 12 U or more PRBCs.



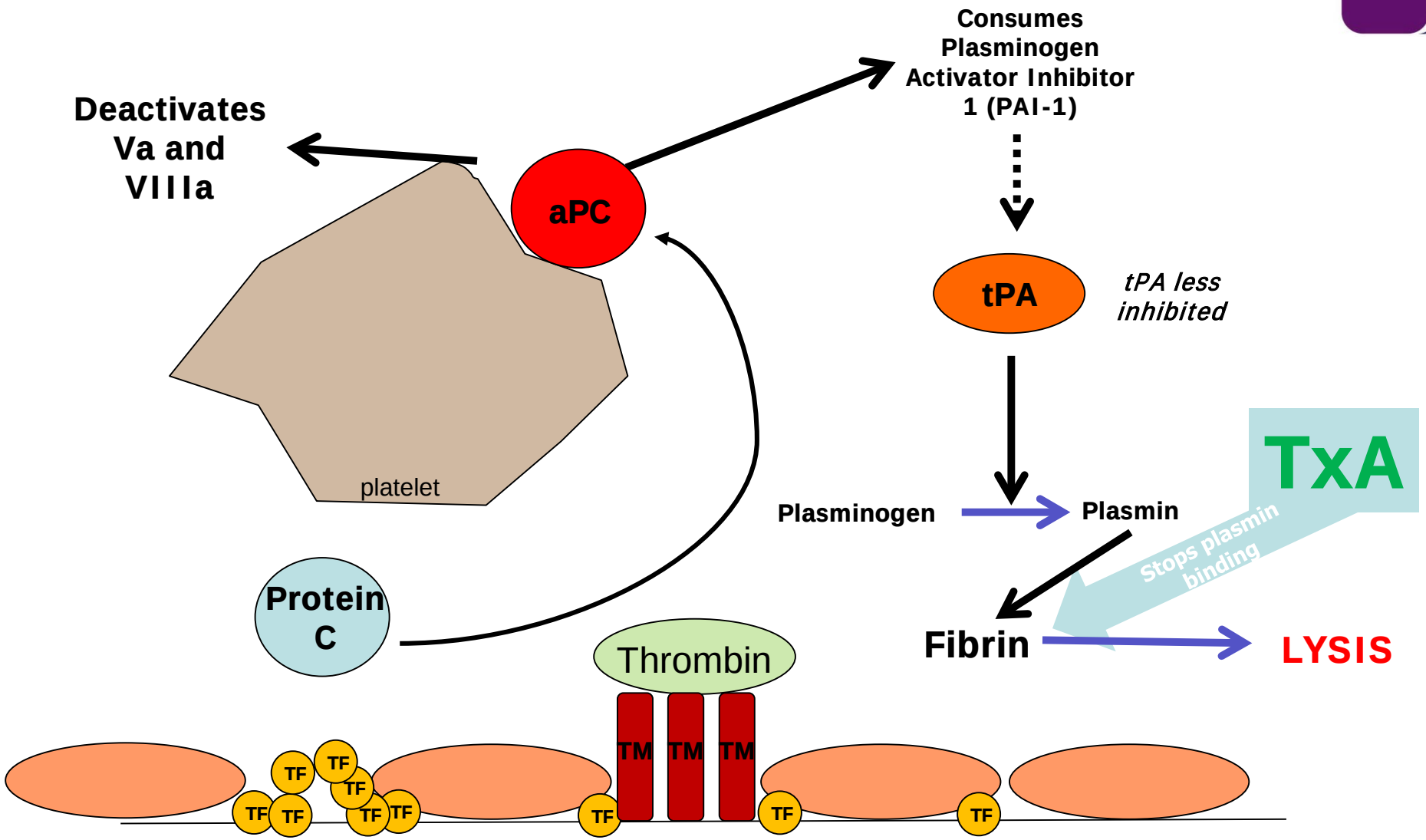




JOINT HEALTH COMMAND

Conventional blood components

Acute traumatic coagulopathy



JOINT HEALTH COMMAND

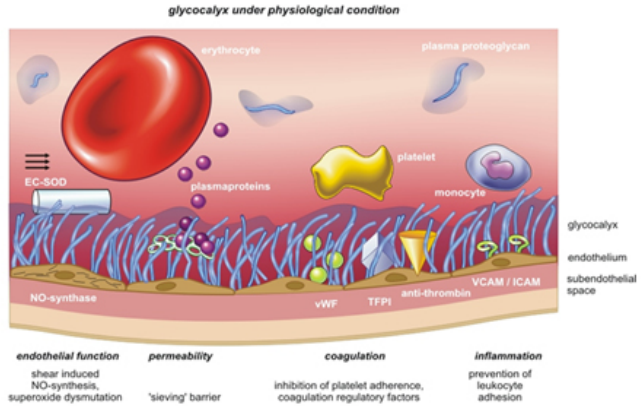
Conventional blood components

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. Sondeen, PhD, Lisa Ji, MD, Michael A. Dubick, PhD, *and* Ivo Torres Filho, MD, PhD, *San Antonio, Texas*

J Trauma Acute Care Surg
Volume 75, Number 5



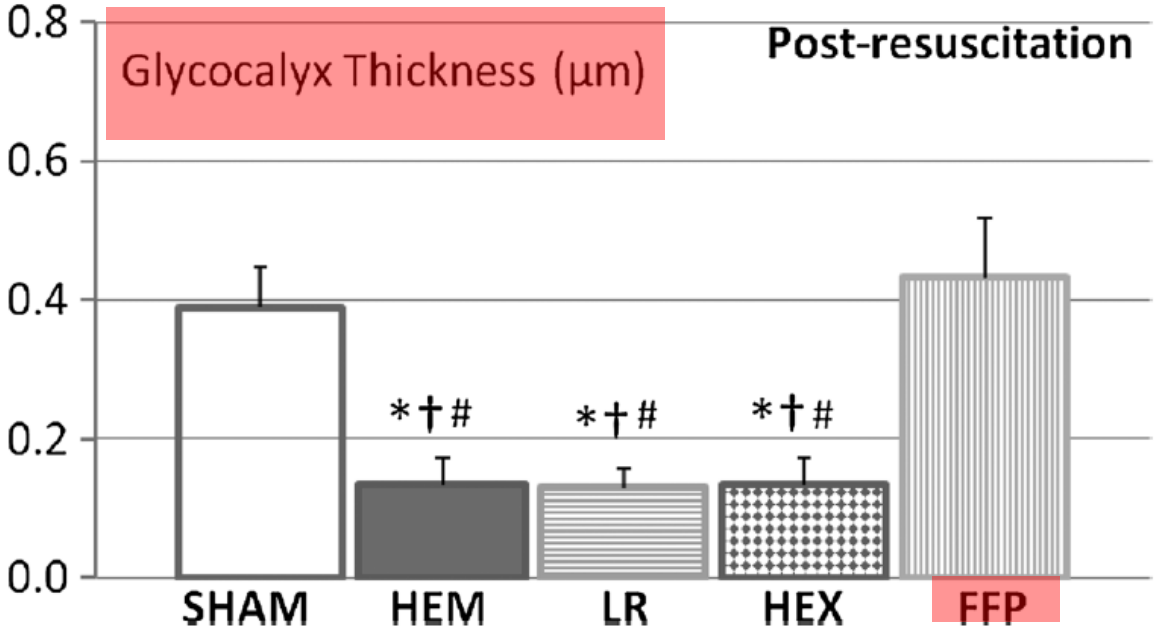


Figure 5. EG thickness in postcapillary venules from cremaster preparations. See Figure 3 for definitions, number of animals,

JOINT HEALTH COMMAND

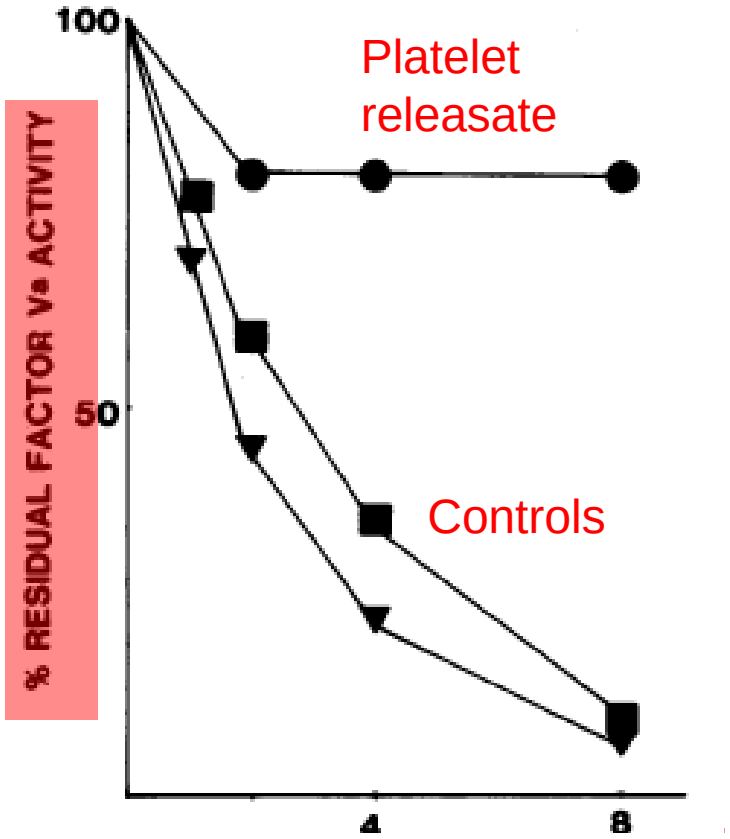
Conventional blood components

Platelet transfusion effects on aPC

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

Effect of platelets on aPC anticoagulant activity:



JOINT HEALTH COMMAND

Conventional blood components: controversies

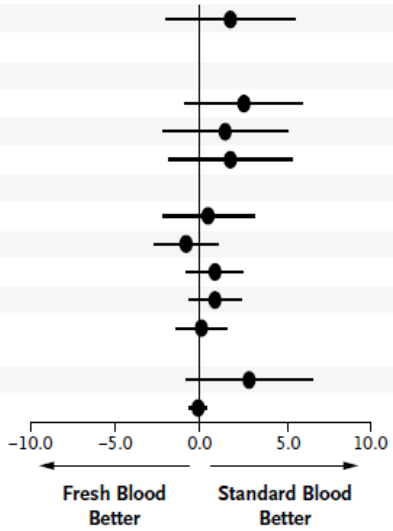
Relevance of the age of PRBCs?

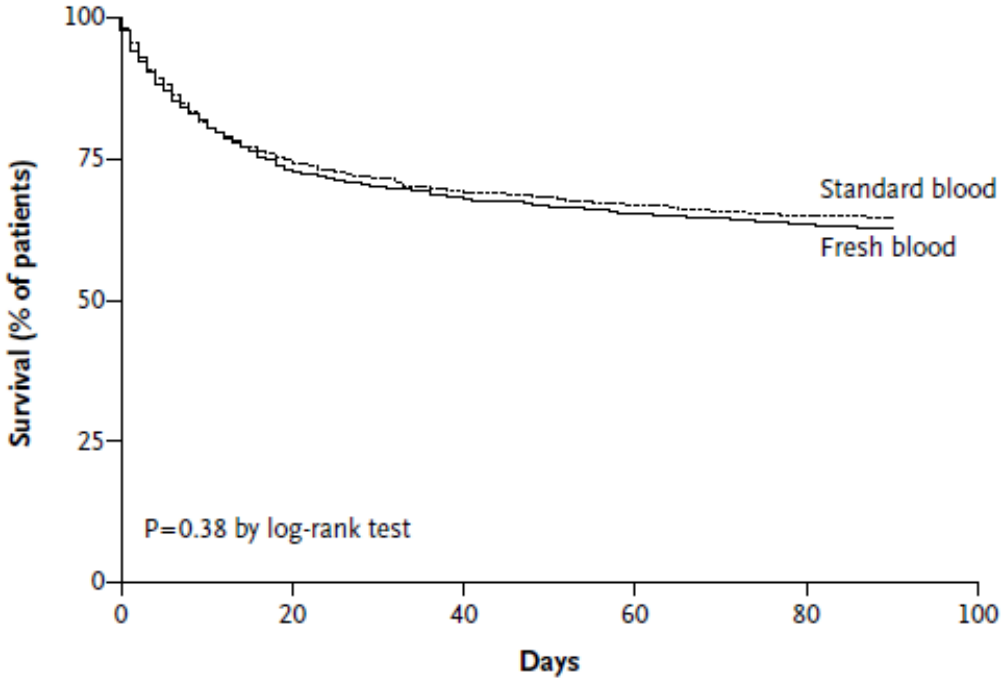
Age of Transfused Blood in Critically Ill Adults

N ENGL J MED 372;15 NEJM.ORG APRIL 9, 2015

the ABLE Investigators and the Canadian Critical Care Trials Group

Outcome	Fresh Blood	Standard Blood	Absolute Risk Difference (95% CI)
	no. of patients/total no. (%)		*percentage points*
Primary outcome: death by day 90	448/1211 (37.0)	430/1219 (35.3)	1.7 (−2.1 to 5.5)
Secondary outcomes			
Death			
In ICU	324/1214 (26.7)	295/1217 (24.2)	2.5 (−1.0 to 5.9)
In hospital	403/1212 (33.3)	386/1211 (31.9)	1.4 (−2.3 to 5.1)
By day 28	371/1214 (30.6)	353/1225 (28.8)	1.7 (−1.9 to 5.4)
Major Illnesses			
Multiple organ dysfunction syndrome	162/1206 (13.4)	157/1207 (13.0)	0.4 (−2.3 to 3.1)
Acute respiratory distress syndrome	69/1206 (5.7)	80/1207 (6.6)	−0.9 (−2.8 to 1.0)
Cardiovascular failure	61/1206 (5.1)	51/1207 (4.2)	0.8 (−0.8 to 2.5)
Cardiac ischemia or infarction	54/1206 (4.5)	44/1207 (3.6)	0.8 (−0.7 to 2.4)
Deep-vein thrombosis or pulmonary embolism	43/1206 (3.6)	43/1207 (3.6)	0.0 (−1.5 to 1.5)
Nosocomial infection	411/1206 (34.1)	378/1207 (31.3)	2.8 (−0.9 to 6.5)
Acute transfusion reaction	4/1206 (0.3)	6/1207 (0.5)	−0.2 (−0.7 to 0.3)





JOINT HEALTH COMMAND

Conventional blood components: controversies

Relevance of the age of PRBCs?

transfuse

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.

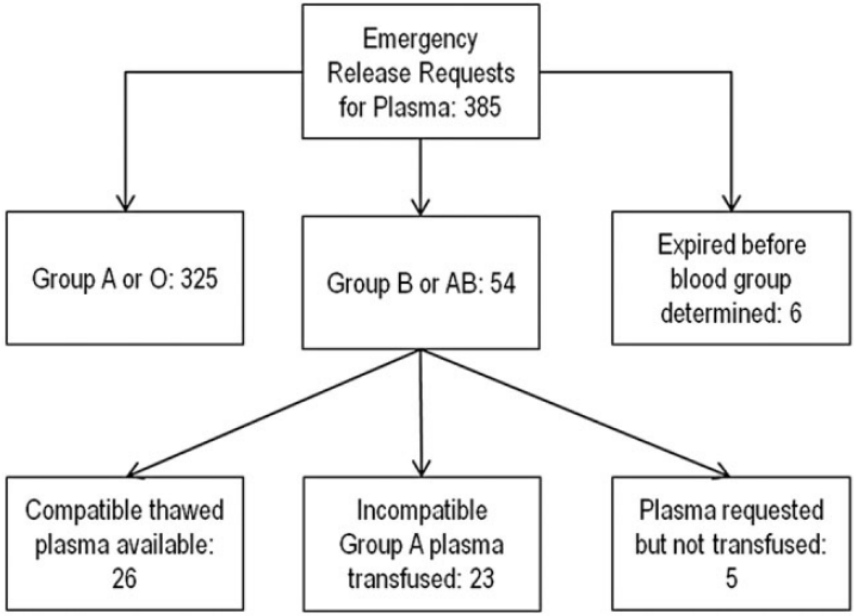
Conventional blood components: controversies

Gp A rather than AB plasma as a universal donor?

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

TRANSFUSION 2014;54:1751-1755.

Vishesh Chhibber,[1,2,3,4,5] Mindy Greene,[4] Michelle Vauthrin,[4] Jeff Bailey,[1,2,4,5] and Robert Weinstein[1,2,3,4,5]

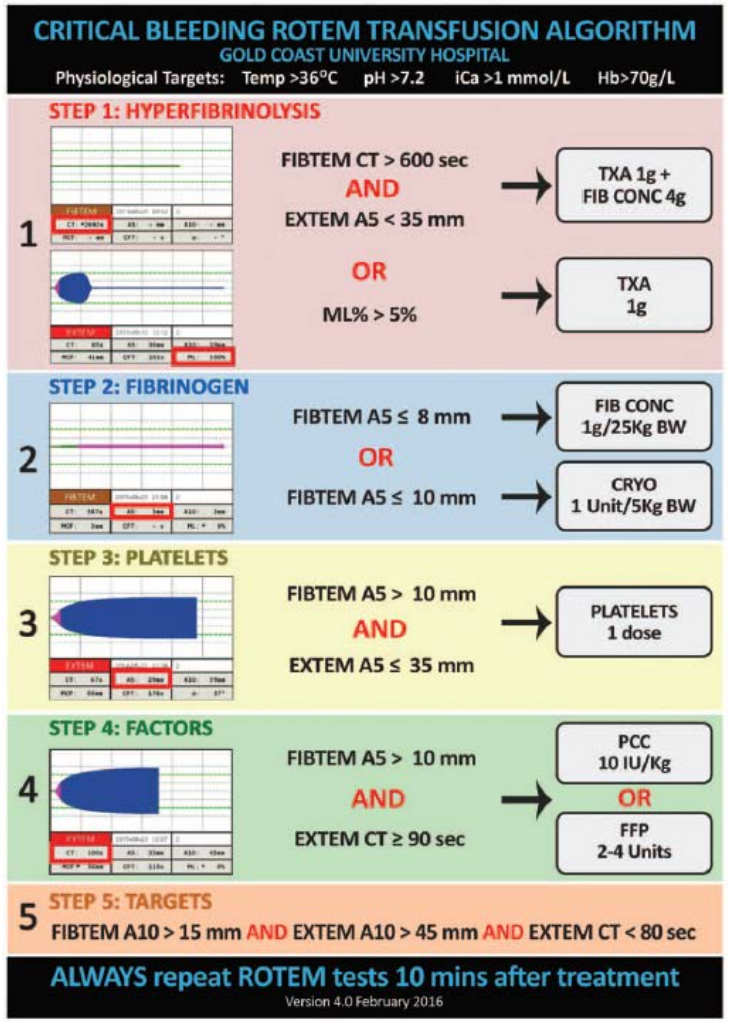


No hemolytic transfusion reactions or other adverse events related to transfusion were seen in any of these 23 patients.

JOINT HEALTH COMMAND

Conventional blood components: controversies

Utility of TEG / ROTEM



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

Curr Opin Anesthesiol 2017, 30:265–276

James Winearls[a,b,c,d], *Biswadev Mitra*[e,f,g], *and Michael C. Reade*[h,i,j]

- 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.

JOINT HEALTH COMMAND

Conventional blood components: controversies

Utility of TEG / ROTEM

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

Verified October 2015 by Queen Mary University of London

Sponsor:
Queen Mary University of London

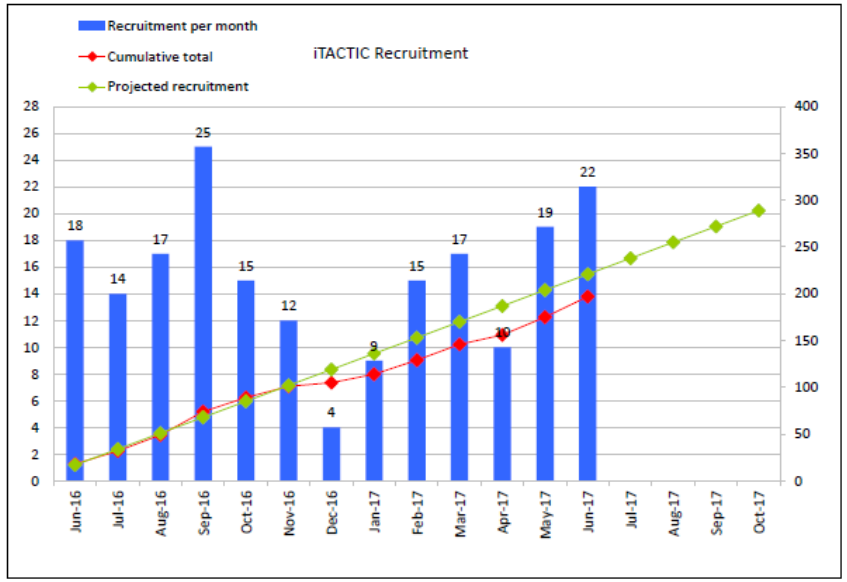
Collaborators:
Oslo University Hospital
Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)
Klinikum der Universität Köln
Rigshospitalet, Denmark
Oxford University Hospitals NHS Trust
Barts & The London NHS Trust
European Commission

ClinicalTrials.gov Identifier:
NCT02593877

First received: October 15, 2015
Last updated: October 30, 2015
Last verified: October 2015
History of Changes

392 patients

Currently recruiting



JOINT HEALTH COMMAND

Current best practice

- **Aim for 1:1:1 ($^{1}/_{5}$)**
- **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

Blood use in war and disaster: lessons from the past century

J.R. Hess and M.J.G. Thomas

TRANSFUSION 2003;43:1622-1633.

The Armed Services Blood Program: Blood support to combat casualty care 2001 to 2011

Francisco Rentas, PhD, David Lincoln, Aaron Harding, Peter Maas, Joseph Giglio, Ronny Fryar, Kathleen Elder, Roland Fahie, Kathleen Whitlock, Jerome Vinluan, *and* Richard Gonzales

J Trauma Acute Care Surg
Volume 73, Number 6, Supplement 5

JOINT HEALTH COMMAND

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**

The US Military Experience With Fresh Whole Blood During the Conflicts in Iraq and Afghanistan

Mark H. Chandler, MD[1], Matthew Roberts, MD, MA, FRCA[1], Mike Sawyer, MD[1], and Greg Myers, MD[1]

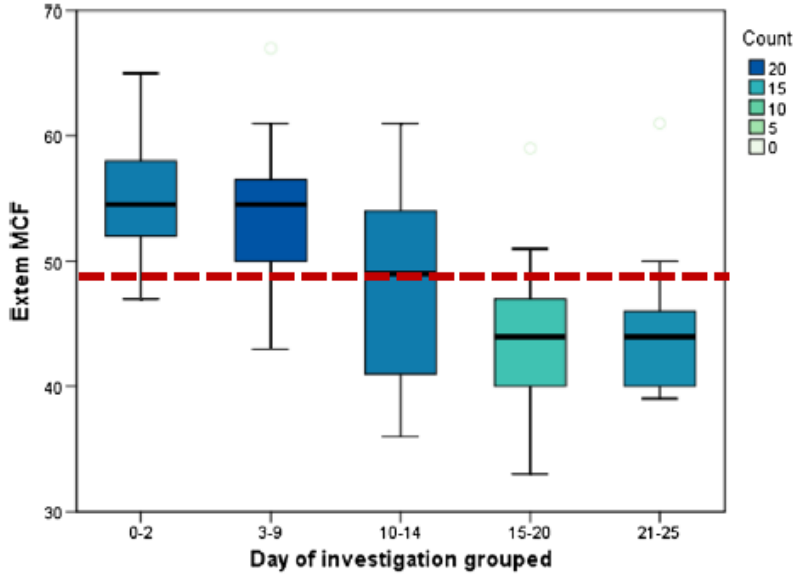
Seminars in Cardiothoracic and Vascular Anesthesia
16(3) 153–159

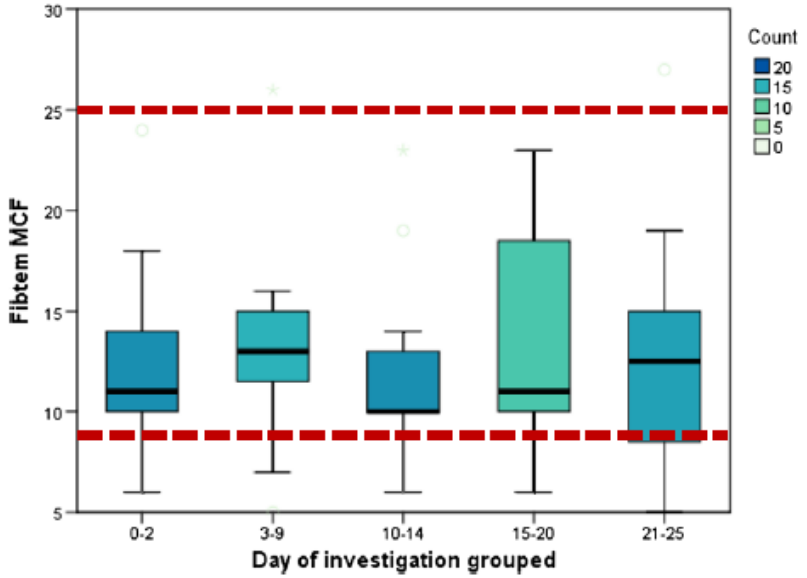
Stored whole blood vs. fresh whole blood

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 F. Pidcoke, MD, PhD, *and* Einar K. Kristoffersen, MD, PhD, *Bergen, Norway*

J Trauma Acute Care Surg
Volume 78, Number 6, Supplement 1





JOINT HEALTH COMMAND

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. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Alec C. Beekley, MD, and John B. Holcomb, MD

J Trauma. 2009;66:S69–S76.

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**

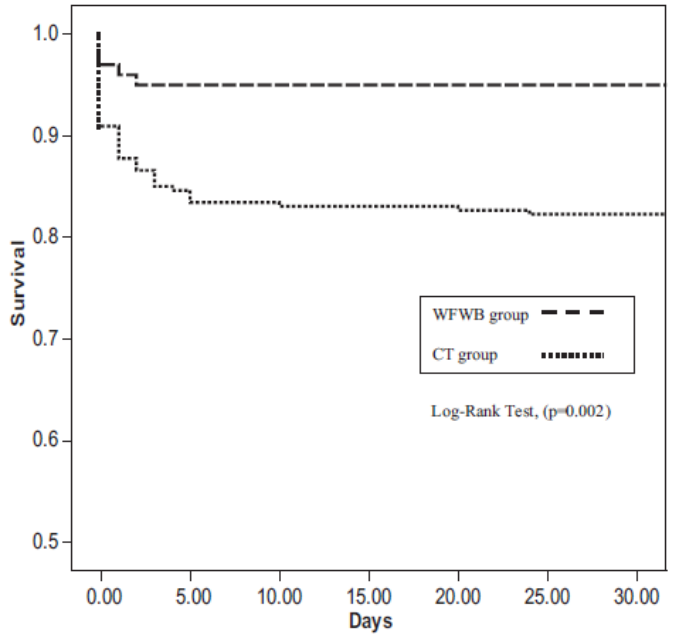


Fig. 1. *Kaplan-Meier curve of 30-day survival according to study group.*

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

Variables	OR (95.0% C.I.)	*p* Value
WFWB group	12.4 (1.8–80)	0.01
Plasma:RBC ratio	11.7 (2.6–52)	0.001
ISS	0.94 (0.91–0.97)	0.001
GCS eyes (normal)	4.1 (1.5–10.8)	0.004
Base deficit	0.88 (0.82–0.95)	<0.001

JOINT HEALTH COMMAND

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,† Jeanette Podbielski, BSN,† Elizabeth Camp, MSPH,† Timothy Welch, NREMT-P,† Deborah del Junco, PhD,† Yu Bai, MD, PhD,† Rhonda Hobbs, MT (ASCP),‡ Jamie Scroggins, MT (ASCP),§ Beth Hartwell, MD,§ Rosemary A. Kozar, MD, PhD,* Charles E. Wade, PhD,*† and John B. Holcomb, MD*† on behalf of The Early Whole Blood Investigators*

(*Ann Surg* 2013;258:527–533)

Single-centre RCT
WB stored up to 5 days
Passed through white cell filter that removed platelets – therefore platelets supplemented

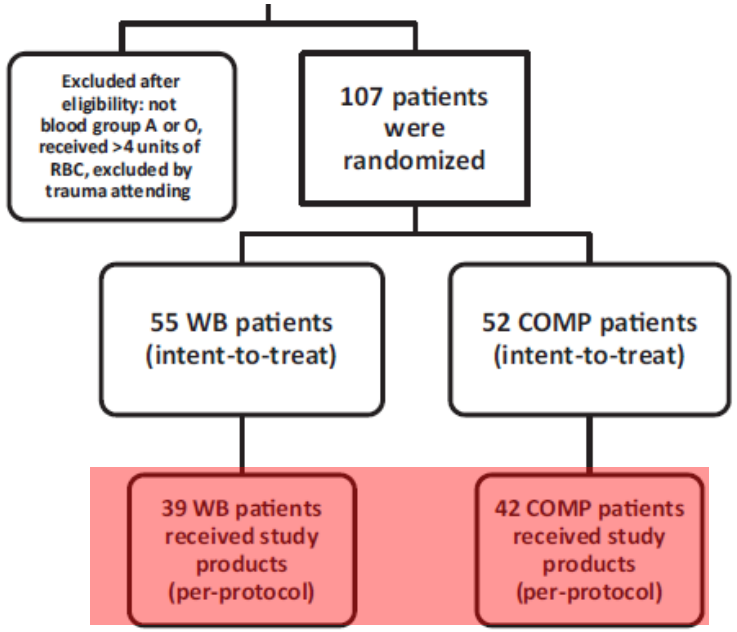


TABLE 2. Primary and Secondary Outcome Differences Among Intent-to-Treat and Per-Protocol Groups

	WB Group	COMP Group	*P*
Intent-to-Treat Group			
n	55	52	
Median 24-hr RBC transfusions, U	4 (2, 8)	6 (2, 11)	0.78
Median 24-hr plasma transfusions, U	4 (2, 8)	4 (2, 10)	0.71
Median 24-hr platelet transfusions, U	0 (0, 1)	0 (0, 2)	0.41
Median 24-hr total transfusions, U	12 (6, 24)	13 (5, 29)	0.61
24-hr mortality, %	11	10	0.83
30-d mortality,%	22	14	0.26
Per-Protocol Group			
n	36	41	
Median 24-hr RBC transfusions, U	6 (3, 9)	6 (4, 13)	0.68
Median 24-hr plasma transfusions, U	6 (3, 12)	6 (4, 13)	0.91
Median 24-hr platelet transfusions, U	1 (0, 2)	1 (0, 2)	0.76
Median 24-hr total transfusions, U	17 (11, 29)	18 (8, 37)	0.99
24-hr mortality, %	16	12	0.58
30-d mortality, %	27	15	0.16

JOINT HEALTH COMMAND

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.**

TRANSFUSION Volume 52, May 2012

Arguments for low-titre O as a universal donor

LOW TITER GROUP O WHOLE BLOOD IN EMERGENCY SITUATIONS

Geir Strandenes,[*†] Olle Berséus,[‡] Andrew P. Cap,[§] Tor Hervig,[*‖] Michael Reade,[¶] Nicolas Prat,[§**] Anne Sailliol,[††] Richard Gonzales,[‡‡] Clayton D. Simon,[§§] Paul Ness,[‖‖] Heidi A. Doughty,[¶¶] Philip C. Spinella,[§***] and Einar K. Kristoffersen[*‖]

Readily available due to high frequency of low-titer group O donors (approximately 95%–70% of group O donors if IgG <400, IgM <100)

A properly-powered whole blood trial?

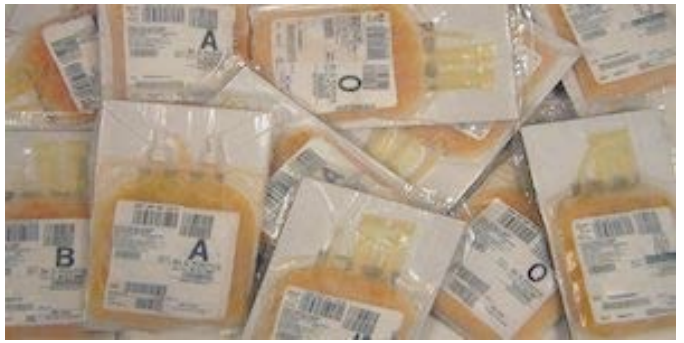
- **Several observational studies suggest fresh whole blood is associated with better outcomes … but residual confounding remains likely.**
- **One underpowered clinical trial showed no benefit**
- **In vitro assessments of stored whole blood suggest cold storage up to 21 days preserves adequate haemostatic 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

MONASH University

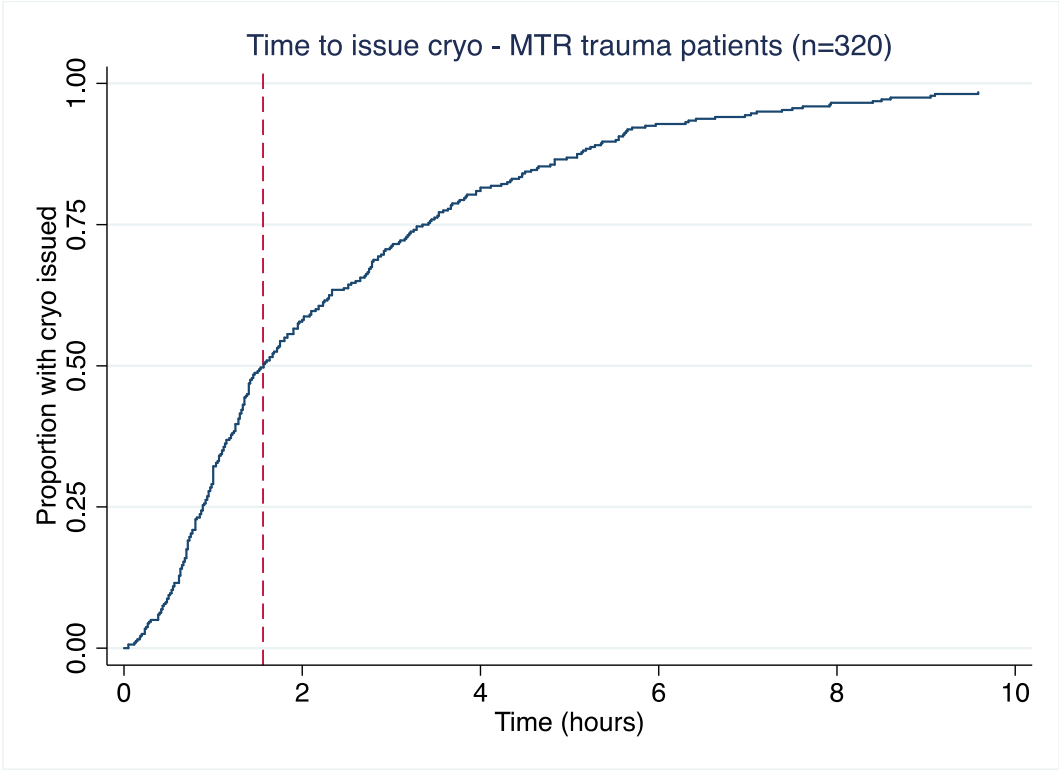
Blood-CRE
Centre of Research Excellence for Patient Blood Management in Critical Illness and Trauma

massive transfusion registry

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



JOINT HEALTH COMMAND

Fibrinogen concentrate: observational studies

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

Arasch Wafaisade, MD, Rolf Lefering, PhD, Marc Maegele, MD, Thomas Brockamp, MD, Manuel Mutschler, MD, Sven Lendemans, MD, Marc Banerjee, MD, Bertil 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^-).

	Fibrinogen Group (FC^+)	Control Group (FC^-)	*p*
Ventilator days, mean ± SD, d	12.2 ± 14.2	11.3 ± 14.7	0.06
ICU LOS, mean ± SD, d	17.2 ± 17.6	17.3 ± 17.9	0.68
Hospital LOS, mean ± SD, d	34.6 ± 33.3	32.8 ± 28.4	0.96
Thromboembolic event, %	6.8	3.4	0.06
Sepsis, %	20.7	17.7	0.35
Organ failure, %	73.8	61.9	0.002
Multiple organ failure, %	61.2	49.0	0.003
Time to death, mean ± SD, d	7.5 ± 14.6	4.7 ± 8.6	0.006
6-h mortality, %	10.5	16.7	0.03
24-h mortality, %	13.9	18.4	0.15
30-day mortality, %	27.9	24.8	0.40
In-hospital mortality overall, %	28.6	25.5	0.40

FC:

- **Lower 6 hour mortality**
- **Delayed death**
- **Higher rates of thromboembolic events and organ failure**

JOINT HEALTH COMMAND

Systematic review of fibrinogen in bleeding patients (in general)

Fibrinogen concentrate in bleeding patients (Review)

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

THE COCHRANE COLLABORATION®

Published:
29 August 2013

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)

Fibrinogen concentrate: clinical reality and cautious Cochrane recommendation

S. Kozek-Langenecker[1*], D. Fries[2], D. R. Spahn[3] and K. Zacharowski[4]

British Journal of Anaesthesia Page 1 of 4
doi:10.1093/bja/aeu004

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-Langenecker[1*], D. Fries[2], D. R. Spahn[3] and K. Zacharowski[4]

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-Glane, 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.

Systematic review of fibrinogen in bleeding patients (in general)

A scientific journals' duty of neutrality

doi:10.1093/bja/aev087

B. von Bormann[1,*], S. Suksompong[1], W. Schleinzer[2], and R. Zander[3]

The authors in question[2] – 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,[3 4] 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?**
- **Procoaguopthy / thrombo-embolic disease?**
- **Multiple donors?**
- **Studies showing improved viscoelastic results with fibrinogen administration may misrepresent in vivo coagulopathy.**

Theoretical problems with fibrinogen concentrate: cost

NATIONAL BLOOD AUTHORITY AUSTRALIA

Fibrinogen concentrate (plasma derived – imported)	RiaSTAP	1g	CSL Behring	$740.50

Clinical fresh frozen plasma (FFP)	WB clinical FFP	295ml+/–10% [2]	Australian Red Cross Blood Service	$304.22
Cryoprecipitate	WB cryoprecipitate	30–40ml [2]	Australian Red Cross Blood Service	$177.15
Cryoprecipitate	Apheresis cryoprecipitate	54–66ml [2]	Australian Red Cross Blood Service	$314.25

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)

JOINT HEALTH COMMAND

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 Ghasabyan,†‡ Eduardo Gonzalez,* Max V. Wohlauer,* Angela Sauaia,*‡ Anirban Banerjee,‡ and Christopher C. Silliman‡§‖

SHOCK, Vol. 41, No. 1, pp. 33–39, 2014

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

	Normal (n = 10)	Heparin (n = 10)	Fibrinogen (n = 10)	Heparin + fibrinogen (n = 10)
R time, min	8.51 ± 0.69	15.53 ± 1.48*	5.93 ± 0.19*	9.57 ± 0.52
k Time, min	3.16 ± 0.3	6.99 ± 0.51*	2.22 ± 0.16*	4.92 ± 0.75
α Angle, degrees	51.74 ± 2.1	30.27 ± 1.78*	58.01 ± 2.18*	41.03 ± 3.14*
MA, mm	60.48 ± 1.43	52.79 ± 1.5*	67.53 ± 1.19*	61.39 ± 1.29
G, dyn/cm^2	7.81 ± 0.45	5.68 ± 0.32*	10.58 ± 0.52*	8.08 ± 0.41
Thrombus generation, mm/min	736.2 ± 18.1	651.7 ± 18.4*	825.9 ± 14.7*	736.2 ± 19.2

The addition of fibrinogen to heparinized blood negated the anticoagulant effects of heparin.

Theoretical problems with fibrinogen concentrate: 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 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

Guideline recommendations: FC / TEG-ROTEM

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

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

Spahn *et al. Critical Care* 2013, 17:R76

Well-designed prospective, randomised double-blinded studies evaluating the effect of fibrinogen supplementation are urgently needed.

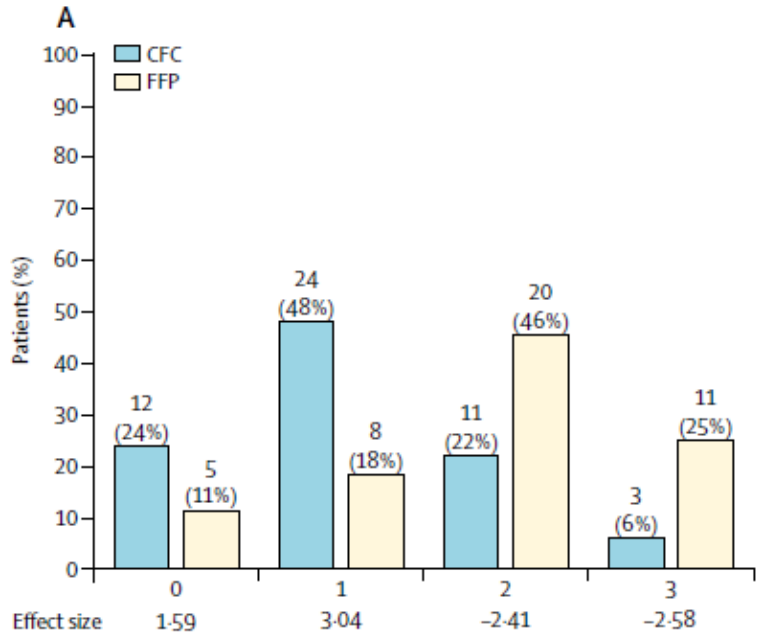
Fibrinogen concentrate: trials completed

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

Petra Innerhofer, Dietmar Fries, Markus Mittermayr, Nicole Innerhofer, Daniel von Langen, Tobias Hell, Gottfried Gruber, Stefan Schmid, Barbara Friesenecker, Ingo H Lorenz, Mathias Ströhle, Verena Rastner, Susanne Trübsbach, Helmut Raab, Benedikt Treml, Dieter Wally, Benjamin Treichl, Agnes Mayr, Christof Kranewitter, Elgar Oswald

. 44 patients in 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

JOINT HEALTH COMMAND

Fibrinogen concentrate: trials completed

ARTICLE

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

N. Curry[1,*], C. Rourke[2], R. Davenport[2], S. Beer[1], L. Pankhurst[3], A. Deary[3], H. Thomas[3], C. Llewelyn[3], L. Green[4], H. Doughty[5], G. Nordmann[6,7], K. Brohi[2], and S. Stanworth[1]

- **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)**

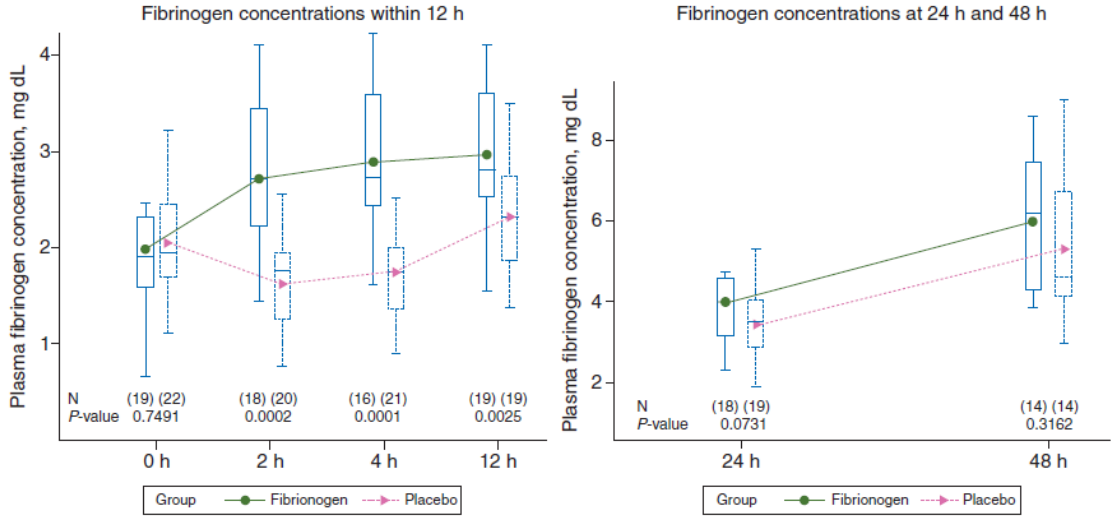
Fibrinogen concentrate: trials completed

Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial

B. Nascimento[1,*], J. Callum[1], H. Tien[1], H. Peng[2], S. Rizoli[3], P. Karanicolas[1], A. Alam[1], W. Xiong[1], R. Selby[1], A-M. Garzon[1], C. Colavecchia[1], R. Howald[1], A. Nathens[1], and A. Beckett[4]

British Journal of Anaesthesia, 117 (6): 775–82 (2016)

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.

JOINT HEALTH COMMAND

Fibrinogen: trials underway

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

JOINT HEALTH COMMAND

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
History of Changes

Completed; not yet published

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
History of Changes

Completed; not yet published

Fibrinogen concentrate: trials underway

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

JOINT HEALTH COMMAND

Courtesy Dr James Winnearls, Gold Coast Hospital Australia

Fibrinogen concentrate: trials underway

Fibrinogen in Trauma (FIT)

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

JOINT HEALTH COMMAND

Courtesy Dr Zoe McQuilten, Monash University Australia

Fibrinogen concentrate: conclusions for now

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

JOINT HEALTH COMMAND

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

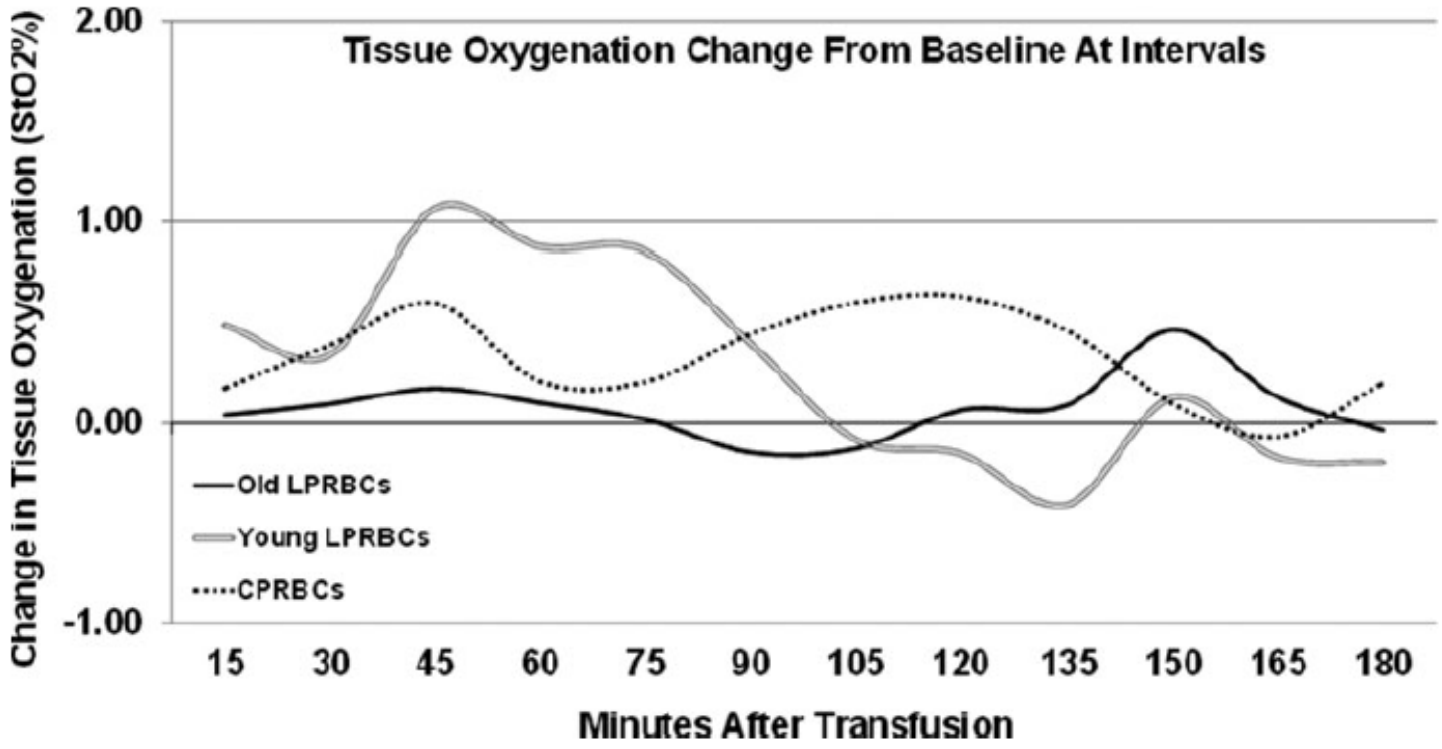
Transfusion of Cryopreserved Packed Red Blood Cells Is Safe and Effective After Trauma

A Prospective Randomized Trial

Martin A. Schreiber, MD, Belinda H. McCully, PhD,* John B. Holcomb, MD,† Bryce R. Robinson, MD,‡ Joseph P. Minei, MD, MBA,§ Ronald Stewart, MD,¶ Laszlo Kiraly, MD,* Nicole T. Gordon, MD,* David T. Martin, MD,* Elizabeth A. Rick, BS,* Rondi K. Dean, BS,* Connor Wiles, BS,* Nathan Anderson, BA,* Dennis Sosnovske, MSEd,* Ben Houser,* Diane Lape, BA,* Bryan Cotton, MD,† Dina Gomaa,‡ Michael W. Cripps, MD,§ Mark DeRosa,¶ and Samantha J. Underwood, MS**

(*Ann Surg* 2015;262:426–433)

256 patients



JOINT HEALTH COMMAND

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. Minei, MD, MBA,§ Ronald Stewart, MD,¶ Laszlo Kiraly, MD,* Nicole T. Gordon, MD,* David T. Martin, MD,* Elizabeth A. Rick, BS,* Rondi K. Dean, BS,* Connor Wiles, BS,* Nathan Anderson, BA,* Dennis Sosnovske, MSEd,* Ben Houser,* Diane Lape, BA,* Bryan Cotton, MD,† Dina Gomaa,‡ Michael W. Cripps, MD,§ Mark DeRosa,¶ and Samantha J. Underwood, MS**

(*Ann Surg* 2015;262:426–433)

256 patients

TABLE 3. Clinical Outcomes

	Old LPRBCs	Young LPRBCs	CPRBCs	*P* (Between Groups)
Total patients	85	82	86	
Acute renal failure	8%	9%	12%	0.45
Acute respiratory distress syndrome	2%	6%	5%	0.46
Ventilator-associated pneumonia	11%	13%	16%	0.28
Infection	26%	30%	28%	0.77
Sepsis	7%	6%	9%	0.58
Deep vein thrombosis	15%	17%	15%	0.97
Pulmonary embolism	7%	4%	6%	0.73
Mortality	3%	4%	4%	0.65

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.

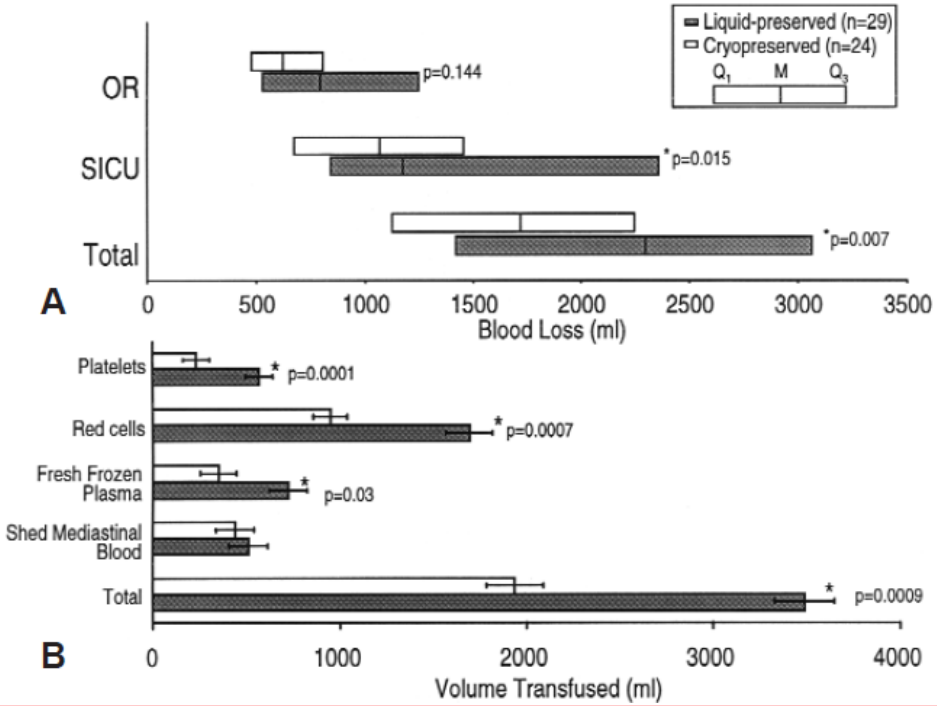
Cryopreserved components

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**

COMPARISON OF THE EFFECTS OF TRANSFUSIONS OF CRYOPRESERVED AND LIQUID-PRESERVED PLATELETS ON HEMOSTASIS AND BLOOD LOSS AFTER CARDIOPULMONARY BYPASS

Shukri F. Khuri, MD[a]
Nancy Healey, BS[a]
Hollace MacGregor, BS[c]
Marc R. Barnard, MS[b]
Irma O. Szymanski, MD[b]
Vladimir Birjiniuk, MD[a]
Alan D. Michelson, MD[b]
David R. Gagnon, MD, MPH, PhD[d]
C. Robert Valeri, MD[c]



JOINT HEALTH COMMAND

Cryopreserved components

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

Femke Noorman[1☯‡*], Thijs T. C. F. van Dongen[2☯‡*], Marie-Christine J. Plat[3], John F. Badloe[1], John R. Hess[4], Rigo Hoencamp[5]

PLOS ONE | DOI:10.1371/journal.pone.0168401 December 13, 2016

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.

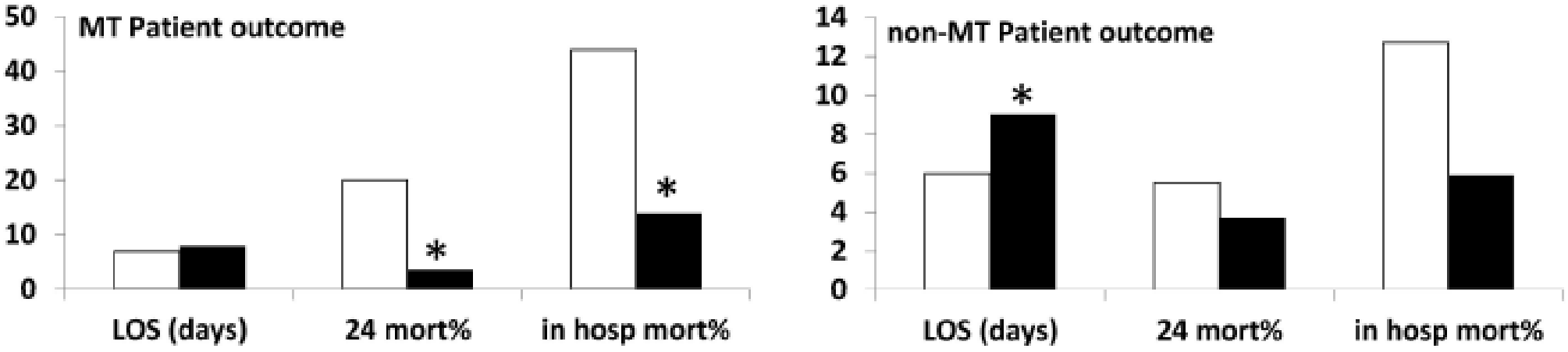


Fig 2. Transfusion, injury and outcome of MT and non-MT patients, pre- and post-MTP. *MT* indicates massive transfusion,

JOINT HEALTH COMMAND

Cryopreserved components

ADF policy decisions:

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

CLIP

Cryopreserved vs. Liquid Platelets for surgical bleeding

THE TECHNICAL COOPERATION PROGRAM

TTCP

JOINT HEALTH COMMAND

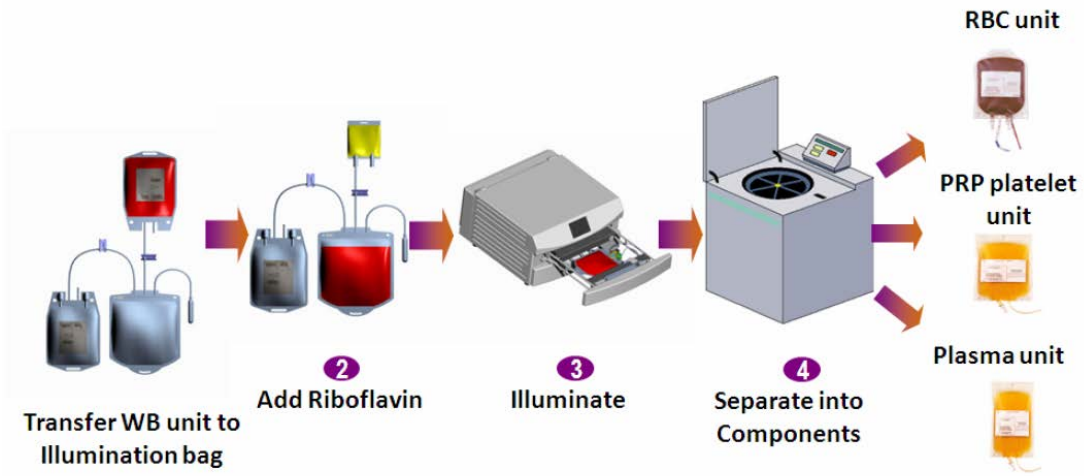
Possible future developments

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

TERUMOBCT



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

Pathogen	Disease/model for	Mirasol PRT System for Platelets and Plasma
HIV: intracellular cell-associated	AIDS	4.5±0.4 5.9±0.2
Porcine Parvovirus	Parvovirus B-19	≥ 5.0
West Nile Virus	HCV	≥ 5.1
Babesia microti	Babesiosis	≥ 4
Trypanosoma cruzi	Chagas' disease	≥ 5
Leishmania donovani	Leishmaniasis	≥ 4
Plasmodium falciparum	Malaria	≥ 3.2
Yersinia enterocolitica	n/a	No regrowth

JOINT HEALTH COMMAND

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 Spreafico, Daniele Prati

Department of Transfusion Medicine and Hematology, Azienda Socio Sanitaria Territoriale (ASST) di Lecco, Alessandro Manzoni Hospital, Lecco, Italy

F1000Research 2017, 6(F1000 Faculty Rev):95

Australian Red Cross BLOOD SERVICE

JOINT HEALTH COMMAND

Table 2. List of *in vitro* experiments comparing platelet storage at 4°C versus room temperature.

Authors	Journal	Year	4°C versus room temperature
Johnson *et al.*[18]	*Transfusion*	2016	Reduction of glycolysis Increased expression of P-selectin Faster thrombin generation Faster clot formation, equal strength
Bynum *et al.*[22]	*Transfusion*	2016	Less oxidative stress Stronger clot Increased response to aggregating agents Better aggregation in shear stress conditions
Getz *et al.*[6]	*Transfusion*	2016	No difference in platelet content in the first 5 days of storage No difference in rotation thromboelastometry (ROTEM) pattern after 5 days of storage
Wood *et al.*[10]	*Transfusion*	2016	Decreased expression of GPIB, GPIX, GPIIB, and GPIV (easier von Willebrand factor attack) Increased expression of P-selectin, tetraspanin, and phosphatidylserine Cytoskeleton protein modifications corresponding to activation state (proteomics) Increased expression of CD62P, CD63, and annexin V
Baimukanova *et al.*[15]	*Transfusion*	2016	Increased aggregation potential
Reddoch *et al.*[9,17]	*Shock* *Shock*	2014 2016	Increased expression of CD40 and P-selectin Increase of intracellular free calcium Increase 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
Mondoro and Vostal[23]	*Platelet*	2002	Increased response to ADP and epinephrine Stronger clot resistance to disaggregating agents No spontaneous aggregation
Connor *et al.*[12]	*Transfusion*	1996	Reduced expression of GMP-140 ADP response of 250%; collagen response of 100% at more than room temperature
Triulzi *et al.*[11]	*Transfusion*	1992	Increased expression of GMP-140
Rinder *et al.*[7]	*Transfusion*	1990	Increased expression of GMP-140
Becker *et al.*[16]	*Transfusion*	1983	More pronounced ADP response

Lyophilised plasma

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

Anne Sailliol, Christophe Martinaud, Andrew P. Cap, Corinne Civadier, Benoit Clavier, Anne-Virginie Deshayes, Anne-Christine Mendes, Thomas Pouget, Nicolas Demazeau, Marine Chueca, François-Régis Martelet, and Sylvain Ausset

TRANSFUSION 2013;53:65S-71S.

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

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

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.

JOINT HEALTH COMMAND

MEDICAL RESEARCH & MATERIEL COMMAND
U.S.ARMY MEDICAL DEPARTMENT

Vascular SOLUTIONS

“Artificial” platelets

Alternatives to allogeneic platelet transfusion

British Journal of Haematology, 2016, **175**, 381–392

Michael J. R. Desborough,[1,2] Peter A. Smethurst,[3] Lise J. Estcourt[1,2] and Simon J. Stanworth[1,2]

Platelet transfusion alternative	Stage of development
Lyophilised platelets	Not in clinical use.
(NCT02223117)	Dose escalation study in healthy volunteers underway.
Haemostatic particles	Not in clinical use.
Coller *et al* (1992), Levi *et al* (1999)	Animal trials only
Liposomes	Not in clinical use.
(Hagisawa *et al* (2015)	Animal trials only
Engineered nanoparticles	Not in clinical use.
Lashof-Sullivan *et al* (2014)	Animal trials only
Infusible platelet membranes	Not in clinical use.
Nasiri (2013)	Limited RCT evidence in thrombocytopenic patients
Platelets generated from stem cells	Not in clinical use
Moreau *et al* (2016)	Animal trials only

“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 Jutkowitz, VMD, DACVECC

Animals – Thirty-seven dogs with a complaint of hemorrhage associated with thrombocytopenia (platelet count $<70 \times 10^9$/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.

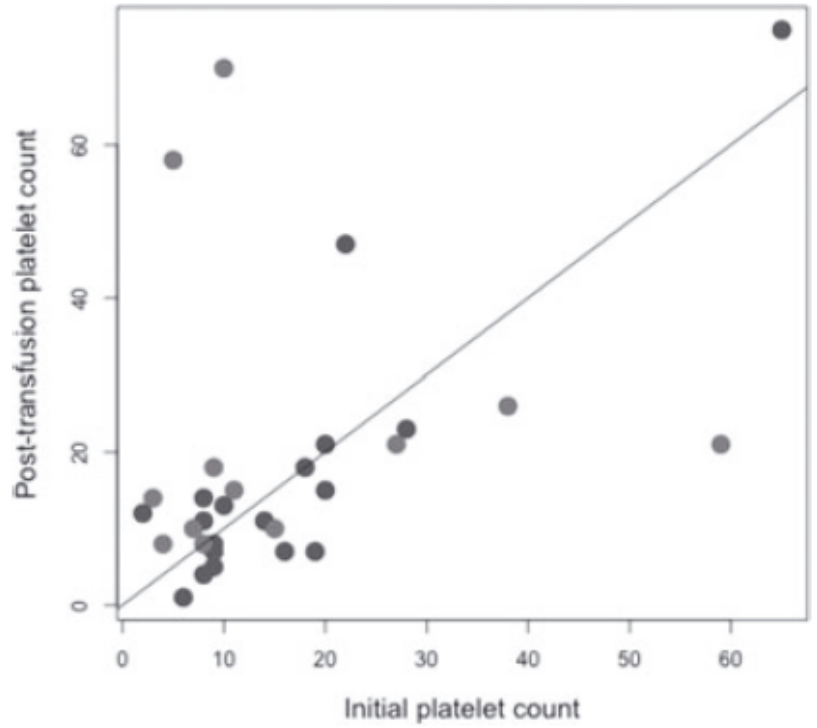
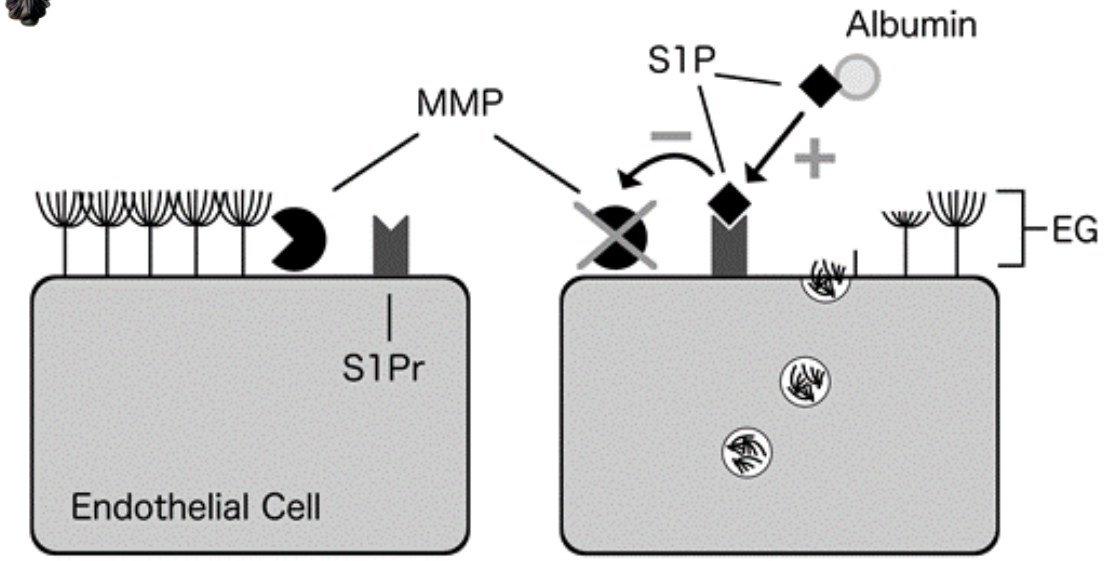


Figure 1: Platelet count following platelet product administration. The line indicates no change in platelet count ($\times 10^3$/μL) with transfusion. Dots to the left of line indicate that the platelet count increased after transfusion, dots to the right indicate that the count decreased despite transfusion. 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).

S1P-enriched fluids



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.

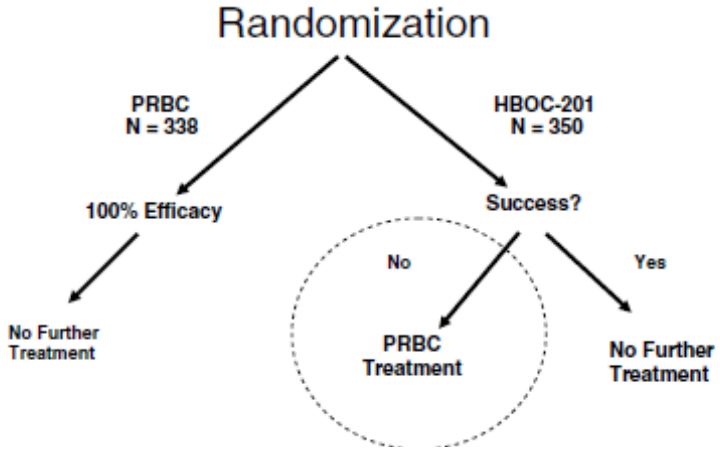
SO: resuscitation with S1P-containing fluids should be the most effective strategy

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. Jahr, MD, Colin Mackenzie, MD, L. Bruce Pearce, PhD, Arkadiy Pitman, MS, and A. Gerson Greenburg, MD, PhD

J Trauma. 2008;64:1484–1497.



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			0.450			0.016			<0.0001			
Treatment Arms												
H	350	0.03	118	88 (25)	0.34 ± 0.04	2,964	334 (95)	8.5 ± 0.3	711	273 (78)	2.0 ± 0.1	
R	338	0.02	83	59 (17)	0.25 ± 0.03	1,987	308 (91)	5.9 ± 0.3				

JOINT HEALTH COMMAND

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

JOINT HEALTH COMMAND