Fibrinogen Concentrate in Trauma

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TMD, St. Mike's
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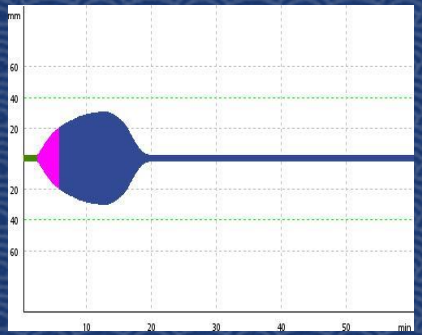
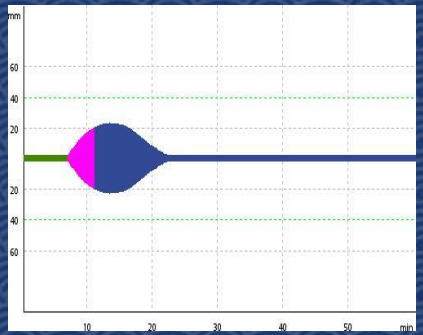
CASE OEF

- Patient came in with uncontrolled bleeding due to gunshot wounds.
- Barely had a radial pulse on pickup.

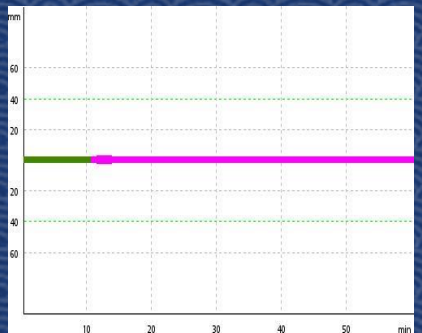
Extem



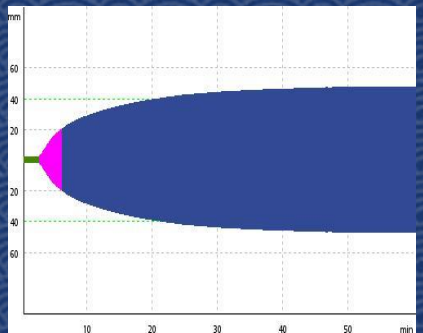
Intem



Fibtem

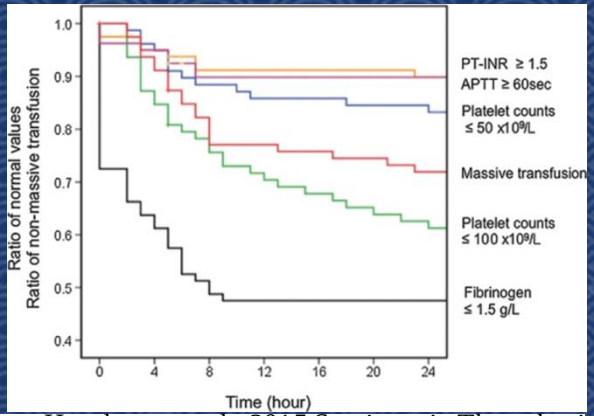


Aptem

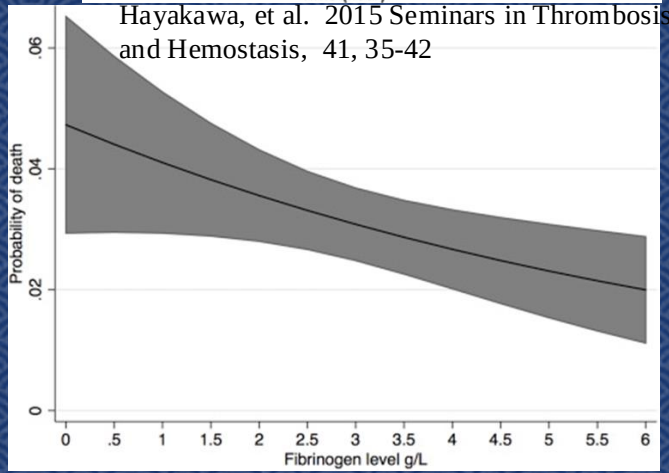


Role of fibrinogen in trauma

- During major bleeding, fibrinogen is the first clotting factor to reach critically low levels, which is associated with increased bleeding, coagulopathy, and in turn worsened clinical outcomes
- Fibrinogen is an independent predictor of mortality in major trauma patients

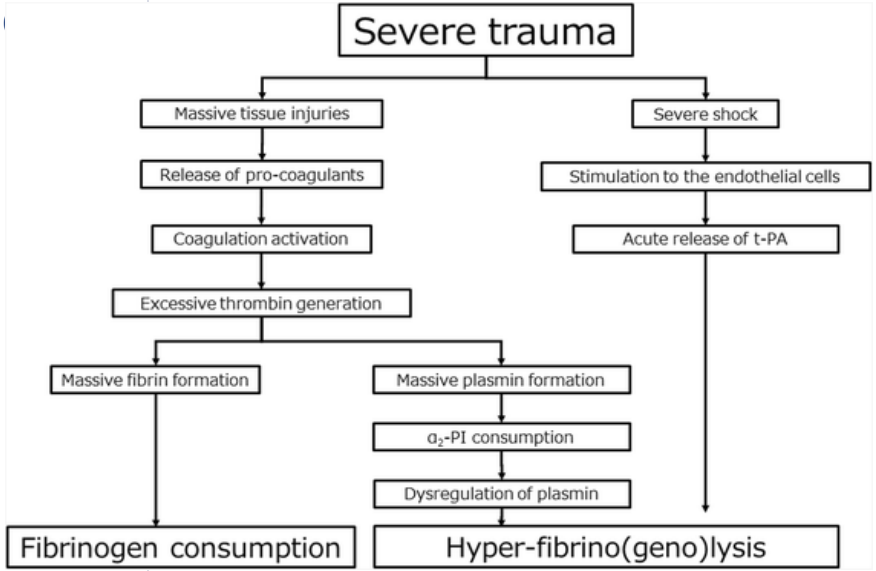


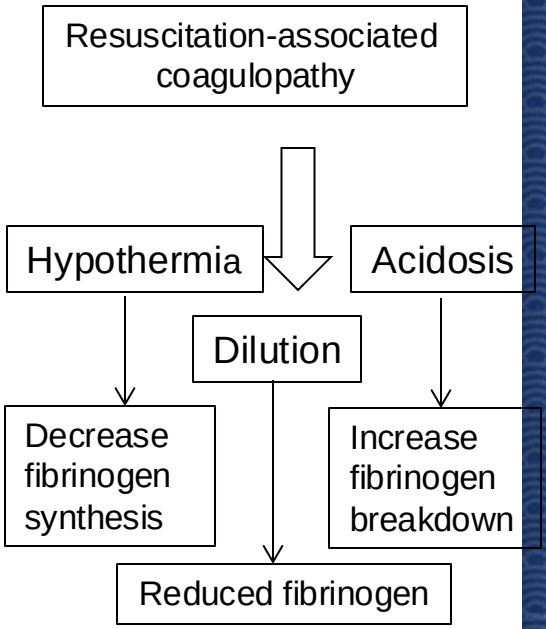
Hayakawa, et al. 2015 Seminars in Thrombosis and Hemostasis, 41, 35-42



McQuilten et al., 2017 Injury, 48(5):1074–1081

Mechanisms for fibrinogen deficien





Hayakawa 2017 Journal of intensive care 5(1):3.

Aubron et al. 2014 Journal of Critical Care29(3):471.e11-471

WHY CHANGE THE WAY WE MANAGE PATIENTS WITH BLEEDING?

- Plasma and cryo do not undergo pathogen reduction
- Plasma not pooled = risk of TRALI
- Plasma needs a blood group – AB plasma in short supply
- Plasma has a high volume (1000 mL/dose)
- Plasma has a low concentration of fibrinogen
- Cryo is difficult and takes time to thaw/pool
- Plasma and cryo can't be stored near patient
- Fibrinogen Concentrate Expensive

OUTLINE

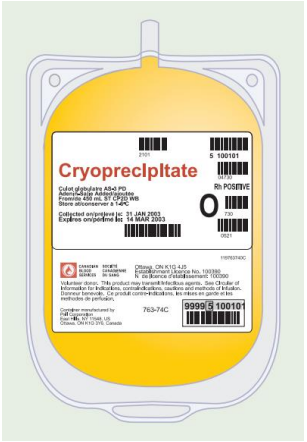
- What products are available and are they safe?
- Status of the evidence?
- Guideline recommendations?

1

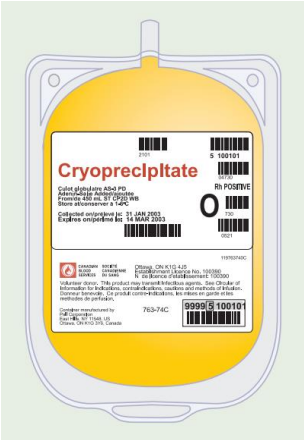
WHAT PRODUCTS ARE AVAILABLE?

And evidence for/against arterial and venous thromboembolism

Fibrinogen OPTIONS



- 250 mL bags
- Dose = 250-500mg of Fibrinogen
- Not pathogen reduced
- Large volume
- AB plasma is the universal donor but only 4% of donors



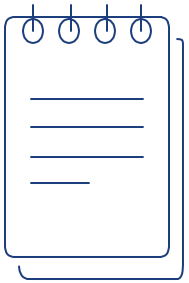
- No longer widely used outside of Quebec, UK and US
- Used primarily for fibrinogen replacement
- 10 U (2 x 5 U bags) adult dose is approximately 2.5-4 g of fibrinogen
- 10 donor exposures
- Not pathogen inactivated

Fibrinogen replacement in trauma

CRYOPRECIPITATE	FIBRINOGEN CONCENTRATE RiaSTAP
Risk of pathogen transmission	Safer; pathogen-inactivated
Withdrawn in European countries due to safety concerns	Licensed for congenital a/hypofibrinogenemia in Canada/US
Preparation (thawing, diluting, pooling)	Preparation (reconstitution with sterile water)
Wide variability in fibrinogen content	Standardized fibrinogen content
Contains other factors (FVIII, vWF, FXIII) Fibronectin 1.5g/L	Fibrinogen Fibronectin 3.5-4g/L
* $2,025 for 15 units (~ 6 grams of fibrinogen)	* $2,094 for 6 grams
Curry 2015 – 85% within 1.5 h	Nascimento 2016 – 96% within 1 h

*Canadian Blood Services 2014

Fibrinogen Concentrates



- Fibrinogen concentrate
  - 2 brands in North America – **RiaSTAP** and Fibryga plus others worldwide

FIBRINOGEN CONCENTRATE

1 GRAM/VIAL
50 mL
4 grams/5 min

10 cryo =
2.5-4.0 g

FIBRYGA (Octapharma)

- Room temperature storage
- Contains more FXIII
- Transfer kit
- 5 minute reconstitution

RiaSTAP (CSL Behring)

- Kept in fridge
- Contains albumin
- Manual transfer
- 15 minute reconstitution once at room temperature

2

WHAT IS THE STATUS OF THE EVIDENCE?

Are concentrates better or not worse than plasma/cryoprecipitate?

CRYO VS. FC SYSTEMATIC REVIEW

1 RCT
3 Obs studies

Comparing efficacy and safety of fibrinogen concentrate to cryoprecipitate in bleeding patients: a systematic review

N. H. L. Jensen[1], J. Stensballe[2,3] and A. Afshari[4]

[1]Department of Anaesthesia, Bispebjerg Hospital, Copenhagen, Denmark
[2]Section for Transfusion Medicine, Capital Region Blood Bank, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[3]Department of Anaesthesia, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[4]Juliane Marie Centre – Department of Anaesthesia, 4013 Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

- No differences in the rate of arterial or venous thromboembolism
- No difference if other safety outcomes (acute kidney injury, length of stay, etc.)

Jensen NH, et al. Acta Anaesthesiol Scand.2016 Sep;60(8):1033-42

FC vs. Cryo

n=43

RCT

Pseudomyxoma Peritonei

All pts got LMWH

- No thromboembolic events were observed in the FC group.
- In the cryo group, 7 patients (30.4%) experienced 7 VTE (5 PE and 2 DVT) – all days 4-11 post-op

Roy A, et al. J Thromb Haemost. 2020;18:352–363

Table III

Factors associated with early VTE (before 12 days) and late VTE (day 12 or later)

Variable	Early VTE		Late VTE	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Cryoprecipitate	1.04 (1.00–1.08)	.03	1.05 (1.01–1.09)	.01
24-h blood product administration				
Red blood cells	0.95 (0.88–1.02)	.18	0.97 (0.89–1.05)	.45
Platelets	0.93 (0.87–1.00)	.04	0.94 (0.86–1.03)	.19
Plasma	1.14 (1.00–1.30)	.05	1.1 (0.96–1.26)	.16
Sepsis	3.05 (1.40–6.64)	.01	2.97 (0.99–10)	.08
Pelvic/femur fracture	2.62 (1.00–6.90)	.05	2.93 (0.90–9.58)	.08
Traumatic brain injury	0.55 (0.21–1.42)	.22	0.21 (0.04–1.10)	.06
Dialysis	2.63 (0.42–16.36)	.30	7.37 (1.59–34.14)	.01
Age	1.00 (0.96–1.05)	.71	1.02 (1.00–1.04)	.05
ICU duration of stay	1.00 (0.96–1.05)	.79	1.08 (1.03–1.13)	.002

2

FIBRINOGEN CONCENTRATES

Trauma and Cardiac

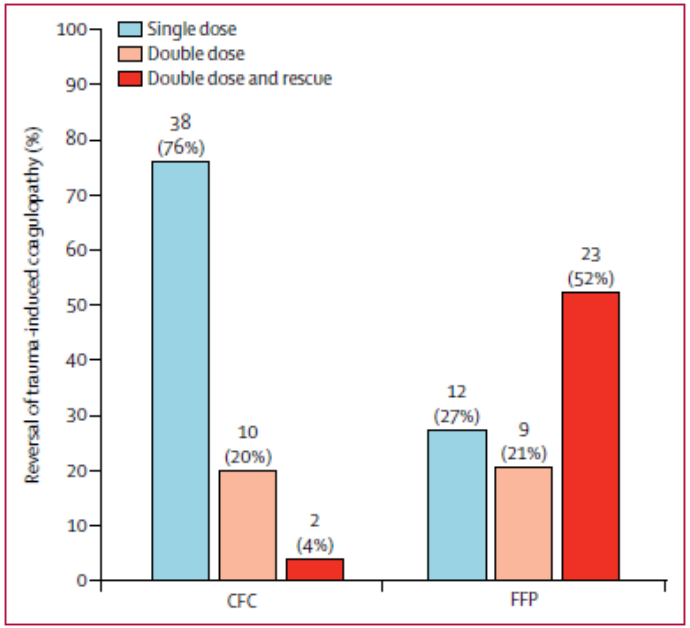
RETIC Study
n=100

Trauma

RCT

ROTEM

FC/PCC vs. plasma



	CFC (n=50)	FFP (n=44)
FFP		
Patients†	2 (4%)	44 (100%)
Dose (U)	5 (5 to 5)	14 (10 to 14)
Fibrinogen concentrate		
Patients†	50 (100%)	23 (52%)
Dose (g)	8 (5 to 10)	5 (4·5 to 8)
Four-factor PCC		
Patients†	8 (16%)	2 (5%)
Dose (IU)	2000 (1875 to 3000)	850 (675 to 1025)
FXIII		
Patients†	27 (54%)	11 (25%)
Dose (IU)	2000 (2000 to 2500)	1500 (1375 to 2000)
Red blood cell concentrate‡		
Patients†	45 (90%)	39 (89%)
Dose (U)	4 (2 to 7)	6 (4 to 11)
Massive transfusion (U)§†	6 (12%)	13 (30%)
Platelet concentrate¶		
Patients†	10 (20%)	21 (48%)
Dose (U)	2 (1 to 4)	2 (1 to 3)

Innerhoffer et al. Lancet Haematol 2017; 4: e258–71

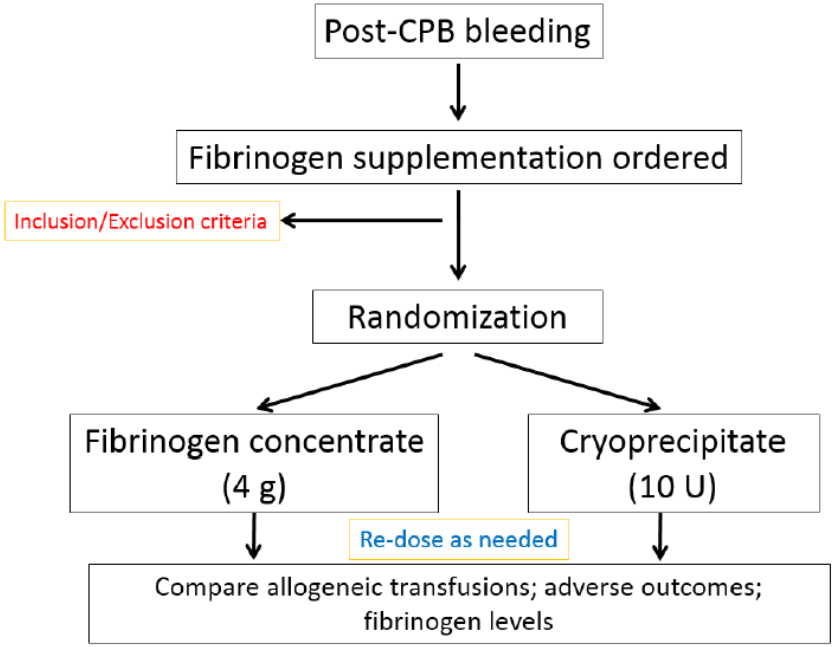
FIBRES Trial

Cardiac Surgery

735 patients

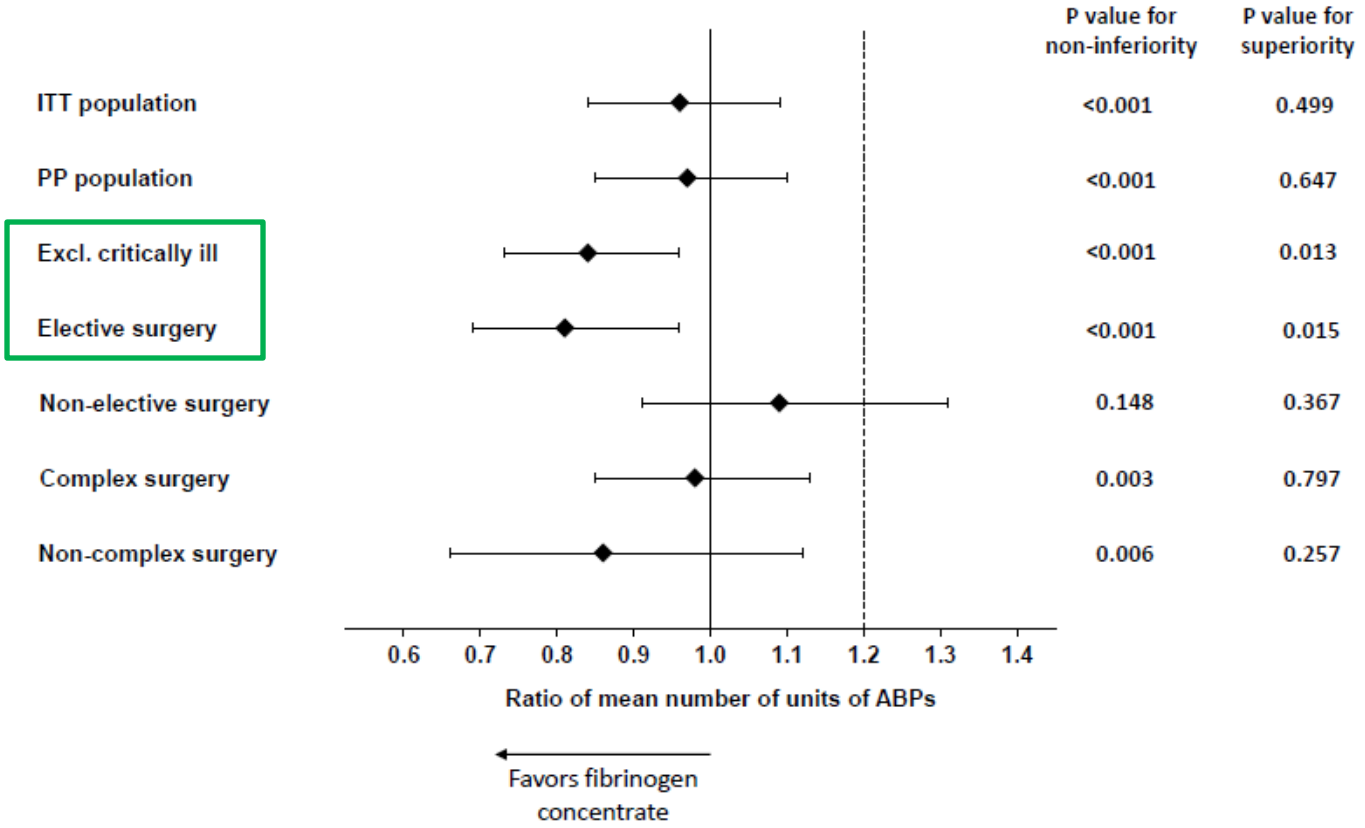
Fibryga

Fibrinogen<2 (or presumed with massive bleeding)



Callum J, et al. *JAMA.* 2019;322(20):1966-1976
Karkouti K et al. BMJ Open.2018 Apr 20;8(4):e020741.

A priori Subgroups



FIBRES

735 patients

Cardiac surgery

Cryo vs. FC

OR 0.70 (0.42-1.20)

Outcome	Fibrinogen Concentrate (N=372)	Cryoprecipitate (N=363)
Any adverse event, No. (%) [No. events]	248 (66.7) [623]	264 (72.7) [673]
Any serious adverse event, No. (%) [No. events]	117 (31.5) [224]	126 (34.7) [264]
Thromboembolic adverse events, No. (%) [No. events]	26[a] (7.0) [27]	35[a] (9.6) [39]
Stroke/TIA	17 (4.6)	18 (5.0)
DVT/PE	5 (1.3)	9 (2.5)
Myocardial infarction	3 (0.8)	4 (1.1)
Other vessel thrombosis	0 (0)	7 (1.9)
Amaurosis fugax	0 (0)	1 (0.3)
Disseminated intravascular coagulation	1 (0.3)	0 (0)
Thrombophlebitis	1 (0.3)	0 (0.0)
Acute kidney injury[b], No. (%)	48 (12.9)	48 (13.2)
Hepatobiliary disorders[c], No. (%)	32 (8.6)	37 (10.2)
Duration of mechanical ventilation, median (IQR), days	1.3 (0.7–5.0) (n=337)	1.3 (0.7–4.2) (n=342)
Duration of intensive care unit stay, median (IQR), days	2.9 (1.4–5.7) (n=352)	2.8 (1.2–5.6) (n=345)
Duration of hospitalization, median (IQR), days	8.2 (6.3–13.0) (n=314)	9.0 (6.3–13.3) (n=308)

Callum J, et al. *JAMA*. 2019;322(20):1966-1976
Karkouti K et al. BMJ Open.2018 Apr 20;8(4):e020741.

Feasibility RCT

BJA

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

doi: 10.1093/bja/aew343
Critical Care

CRITICAL CARE

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]

[1]Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Defence Research and Development Canada, Toronto, ON, Canada, [3]Saint Michael's Hospital, Toronto, ON, Canada and [4]Montreal General Hospital, Montreal, Quebec, Canada

- Randomized placebo controlled trial to investigate safety and feasibility of administrating fibrinogen concentrate within 1 hour of hospital arrival in trauma with risk of severe bleeding
- Included 45 adult trauma patients with risk of severe bleeding as evidenced by a systolic blood pressure ≤ 100 mmHg at any time from injury until 30min after admission and require RBC transfusion

- FiiRST trial confirmed feasibility and safety of administrating fibrinogen within the first hour of hospital arrival in severely injured

BJA

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

doi: 10.1093/bja/aew343

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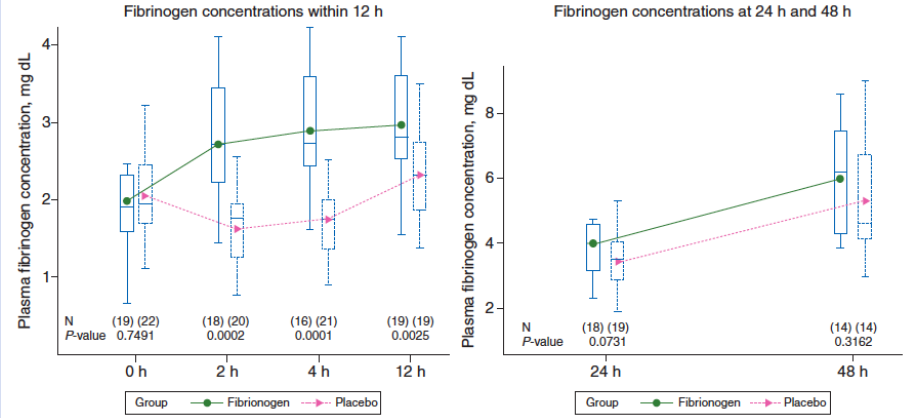


Fig 2 Plasma Fibrinogen Concentrations throughout 48 h of Hospitalization.
Data are presented as means (standard deviation) or median (interquartile ranges)
FC, fibrinogen concentrate

Clinical Findings

- Feasibility
  - 95.6% of patients receiving fibrinogen or placebo within first 1 hour of hospital admission
- Safety
  - No major difference in safety endpoints between fibrinogen and placebo groups
- Clinical outcomes
  - Significant differences in coagulation profiles
  - No difference in blood transfusion (given the small sample size)

EJA

Eur J Anaesthesiol 2021; 38:348–357

OPEN

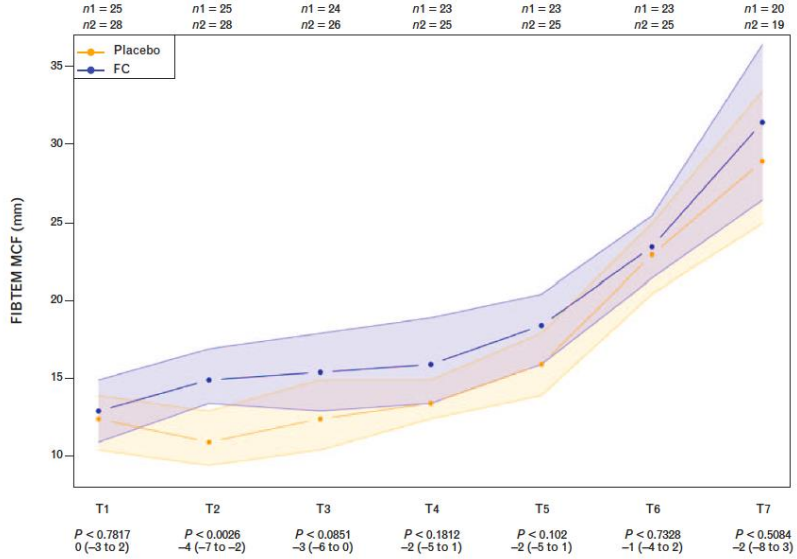
ORIGINAL ARTICLE

Efficacy of prehospital administration of fibrinogen concentrate in trauma patients bleeding or presumed to bleed (FIinTIC)

A multicentre, double-blind, placebo-controlled, randomised pilot study

Bernhard Ziegler, Mirjam Bachler, Hubert Haberfellner, Christian Niederwanger, Petra Innerhofer, Tobias Hell, Marc Kaufmann, Marc Maegele, Uriel Martinowitz, Carolin Nebl, Elgar Oswald, Herbert Schöchl, Bettina Schenk, Markus Thaler, Benjamin Treichl, Wolfgang Voelckel, Ivana Zykova, Christine Wimmer, Dietmar Fries, the FIinTIC study group*

Fig. 3 Changes in FIBTEM maximum clot firmness (FIBTEM MCF) between baseline (T1) and 7 days posttrauma (T7)



Data are presented as median [IQR] (boxes; as well as minimum and maximum plus outliers as dots). *P* values are given with difference between groups and 95% CI. Horizontal dashed red lines show boundaries of the normal range. FC, Factor Concentrate group; n1, Placebo group; n2, FC group.

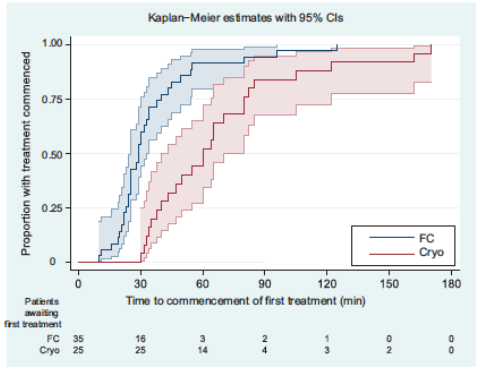
CONCLUSION Early fibrinogen concentrate administration is feasible in the complex and time-sensitive environment of pre-hospital trauma care. It protects against early fibrinogen depletion, and promotes rapid blood clot initiation and clot stability.

Fibrinogen Early In Severe Trauma studY (FEISTY): results from an Australian multicentre randomised controlled pilot trial

James Winearls, Martin Wullschleger, Elizabeth Wake, Zoe McQuilten, Michael Reade, Catherine Hurn, Glenn Ryan, Melita Trout, James Walsham, Anthony Holley, Shane George, Wayne Dyer, James McCullough, Gerben K... John Fraser, Jeffrey Presneill and Don Ca...

Figure 3. Time to commencement of first FC or Cryo treatment*

	Patients receiving intervention	
	FC	Cryo
Patients with FIBTEM A5 ≤ 10 mm	35 (71%)	25 (51%)
Time to FC or Cryo, min	29 (23–40)	60 (40–80)
FIBTEM A5, mm	8 (7–9)	9 (5–10)
First dose of FC, g	3 (2–4)	–
First dose of Cryo, units	–	8 (8–14)



Cryo = cryoprecipitate. FC = fibrinogen concentrate. FIBTEM A5 = functional fibrinogen assessment at 5 minutes after clot formation. * Data in table are

Conclusion: Fibrinogen replacement in severely injured trauma patients with major haemorrhage and hypofibrinogenaemia was achieved substantially faster using FC compared with Cryo. Fibrinogen levels increased appropriately using either product. The optimal method for replacing fibrinogen in traumatic haemorrhage is controversial. Our results will inform the design of a larger trial powered to assess patient-centred outcomes.

BMJ Open

Protocol for a multicentre, randomised, parallel-control, superiority trial comparing administration of clotting factor concentrates with a standard massive haemorrhage protocol in severely bleeding trauma patients: the FiiRST 2 trial (a 2020 EAST multicentre trial)

Luis Teodoro da Luz ,[1,2] Jeannie Callum,[3] Andrew Beckett,[2,4] Hans-Peter Hucke,[5] Jo Carroll,[6] Deep Grewal,[6] Bruce Schwartz,[7] Henry Peng,[8] Paul T Engels,[9] Neil Parry,[10] Andrew Petrosoniak,[11] Homer Tien,[1] Avery B Nathens,[1] Damon Scales,[12] Keyvan Karkouti[13]

Strengths and limitations of this study

- This is the first large randomised controlled trial assessing the early preemptive coadministration of fibrinogen concentrate and prothrombin complex concentrate for haemorrhaging trauma patients.
- The trial is the first one to compare the use of both investigational products with the standard of care, the replacement of clotting factors with a ratio-based plasma resuscitation.
- The use of an active control will permit that all patients receive clotting factors supplementation as clinically indicated.
- Clinicians will not be fully blinded to treatment allocation. However, patients, caregivers, clinical team members involved in care after trauma bay resuscitation and all outcome assessors will be blinded to minimise risk of bias.
- The study design aligns with standard clinical practice which will permit and enhance adherence and ensure clinical relevance and generalisability, while stratified randomisation by participating site is applied to address between-site practice variability.

da Luz LT, *et al*. *BMJ Open* 2021;**11**:e051003. doi:10.1136/bmjopen-2021-051003

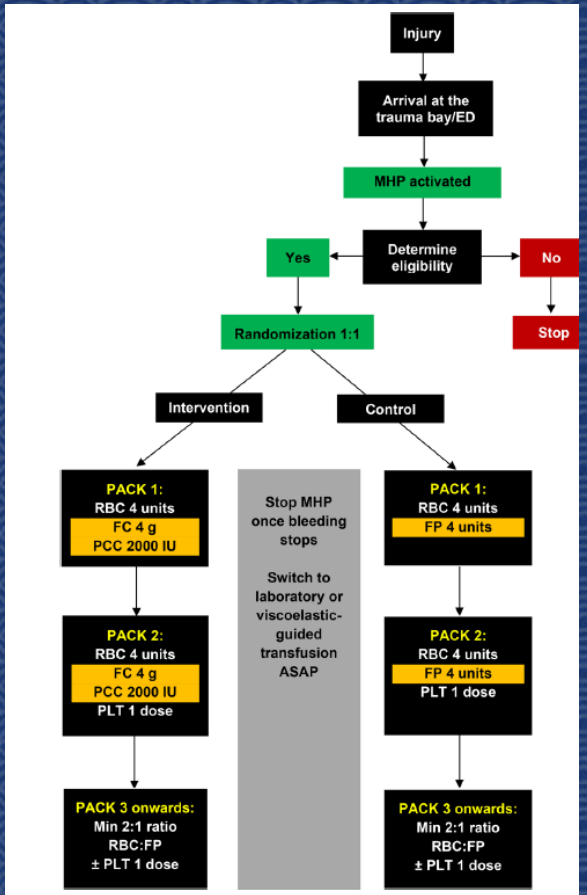


Figure 1 Study design. ED, emergency department; FC, fibrinogen concentrate; FP, frozen plasma; MHP, massive haemorrhage protocol; PCC, prothrombin complex concentrate; PLT, platelets; RBC, red blood cells.

STOP

FUTLITY

3

WHAT DO THE GUIDELINES STATE?

Bleeding Guideline for Critically ill Patients

2021

1. Use RBC:Plasma 2:1 or higher in trauma
2. Suggest using viscoelastic testing for trauma
3. In cardiac surgery use either viscoelastic or conventional tests
4. In cardiac surgery use FC based on testing with either Claus>1.5 or FIBTEM

Vlaar APJ, for European Society of Intensive Care Medicine. Intensive Care Med. 2021 Oct 22:1–25.

Trauma Guideline

2019

European

- We recommend that the use of FFP be avoided for the treatment of low fibrinogen
- Fibrinogen<1.5 g/L -15–20U (=4.8-6.4 g in Canada) cryo or 3–4g FC

Spahn et al. Crit Care. 2019 Mar 27;23(1):98.

GUIDELINES Open Access

The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

Rolf Rossaint[1*], Arash Afshari[2], Bertil Bouillon[3], Vladimir Cerny[4,5], Diana Cimpoesu[6], Nicola Curry[7,8], Jacques Duranteau[9], Daniela Filipescu[10], Oliver Grottke[1], Lars Grønlykke[11], Anatole Harrois[9], Beverley J. Hunt[12], Alexander Kaserer[13], Radko Komadina[14], Mikkel Herold Madsen[2], Marc Maegele[15], Lidia Mora[16], Louis Riddez[17], Carolina S. Romero[18], Charles-Marc Samama[19], Jean-Louis Vincent[20], Sebastian Wiberg[11] and Donat R. Spahn[13]

Fibrinogen supplementation

Recommendation 29 We recommend treatment with fibrinogen concentrate or cryoprecipitate if major bleeding is accompanied by hypofibrinogenemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level ≤ 1.5 g/L) (Grade 1C)*

We suggest an initial fibrinogen supplementation of 3–4 g. This is equivalent to 15–20 single donor units of cryoprecipitate or 3–4 g fibrinogen concentrate. Repeat doses should be guided by VEM and laboratory assessment of fibrinogen levels (Grade 2C).

Rossaint *et al. Critical Care* (2023) 27:80

MILITARY MEDICINE, 183, 1/2:e45, 2018

Fibrinogen Concentrate in the Special Operations Forces Environment

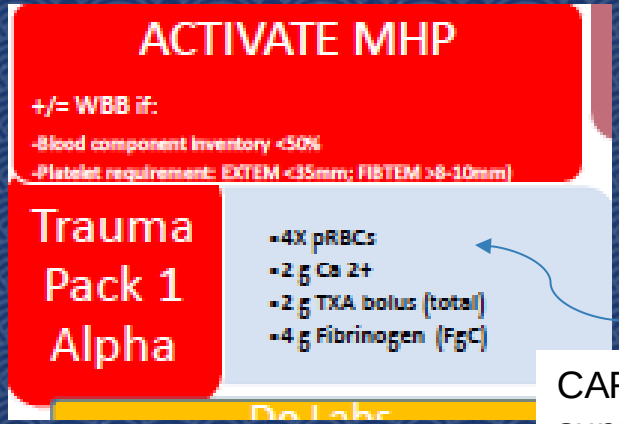
Steven Sanders, BSc; COL Homer Tien, MSc, MD, FRCSC†‡; Jeannie Callum, MD, FRCPC‡; Barto Nascimento, MD‡; Henry Peng, PhD§; Chris Funk, MD†; Joanne Schmid, BScN†; Sandro Rizoli, PhD MD, FRCSC‖; Shawn Rhind, PhD‡; LCOL Andrew Beckett, MD, FRCSC*†*

The CAF adopted Fibrinogen Concentrate (FC) for damage control resuscitation for bleeding patients in the austere far forward combat setting in 2015

TABLE I. Comparison of Fibrinogen Replacement Methods Available to Canada Armed Forces

	FFP[17,18]	Cryoprecipitate[19]	Fibrinogen Concentrate[20]
Fibrinogen content	1–3 mg/mL	Around 15 mg/mL	900–1300 mg/50 mL
Cold chain requirement	Yes	Yes	No
ABO compatibility requirement	Yes	Yes	No
Pathogen risk	Low	Low	Extremely minimal
Shelf life	12 mo (−18°C)	12 mo (−20°C)	60 mo (25°C)[16]
Preparation time	30-min thawing	10-min thawing	5–10 min

Canadian Armed Forces Massive Hemorrhage Protocol



CAF is now supplied LR CWB by Canadian Blood Services

Resuscitation Targets			
Temp >36°C	Fib >1.5	pH >7.2	INR <1.8
iCa2+ >1.15 mmol/L	Plt >75 X10⁹/L	Lactate <4	BE <-6
Hgb >80 g/L	EXTEM CT <90	FIBTEM >8-10MM	

Back to Case

- the patient received:
- 2 unit of Whole blood
- 12 PRBC
- 4 FFP
- 10g Fibrinogen
- No Platelets

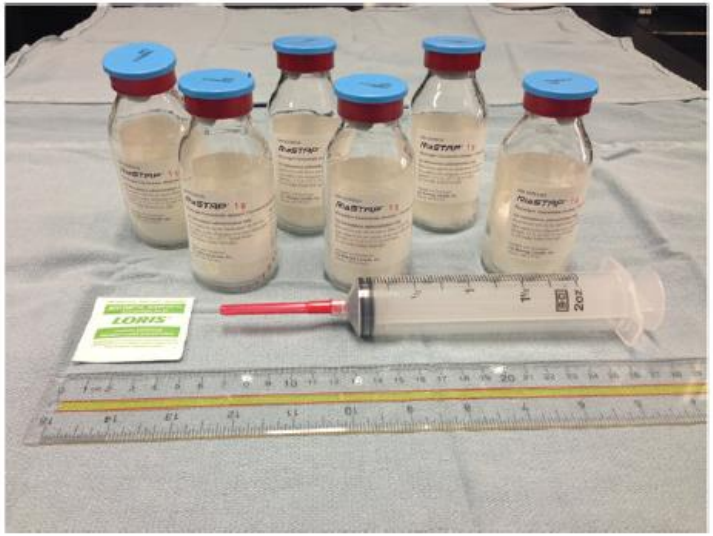
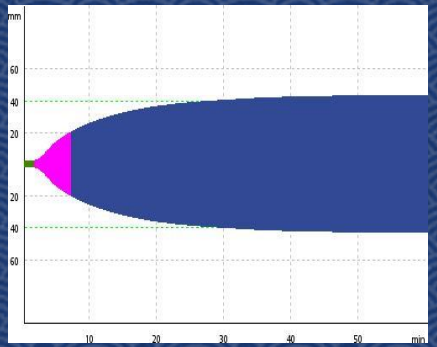


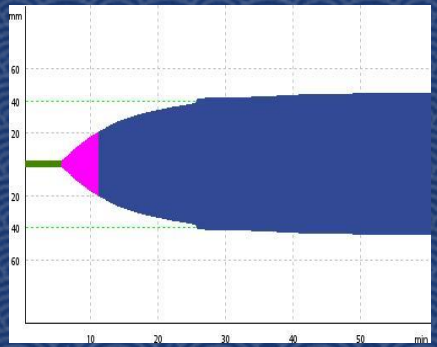
FIGURE 1. Equipment required for the administration of 6 g dose of fibrinogen concentrate: one 60-mL syringe, one 18-gauge blunt fill needle (or equivalent), one alcohol swab, and six 1-g vials of fibrinogen concentrate. Sterile water for reconstitution not shown (RiaSTAP; CSL Behring, Marburg, Germany).

PATENT Guided Resuscitation and Transfusion (4s)

Extem

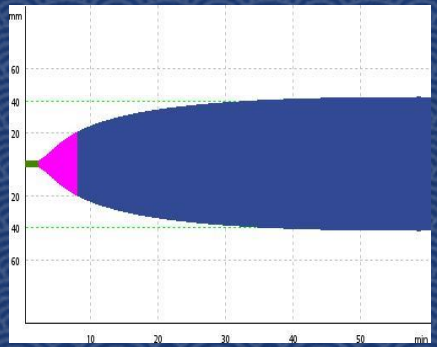


Intem

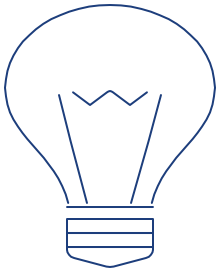


Fibtem

Aptem



SUMMARY



- Numerous studies actively evaluating cryo alternatives
- No obvious increase in VTE with Fibrinogen Cx
- Hemostatically they look at least as good
- Some guidelines support using these products as standard of care
- **Should we only give goal directed Fib Cx vs empiric?**