Fibrinogen concentrate and ROTEM monitoring to guide blood product use

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Disclosures

NONE
My Journey

1. Fibrinogen is central and important
2. Fibrinogen concentrate.
3. ROTEM
4. Life has got much easier now
Fibrinogen is produced by the liver at 2-5g/d and normal plasma levels are 2 to 4.5g/L.

Depletion begins early in cardiac surgery and is exacerbated by dilution, acidosis, hypothermia, and CPB.

Classical coagulation test are NOT useful post cardiac surgery.
Fibrinogen plays a central role in the coagulation process and clot stabilization. Thrombin cleaves fibrinogen to form fibrin polymers that bind factor XIII to form a robust fibrin network. Fibrinogen also induces platelet activation and aggregation by binding to the platelet fibrinogen receptor glycoprotein IIb/IIIa.

FIBTEM allows decreased fibrinogen function to be detected in 10-15 minutes.
COAGULATION CASCADE

Extrinsic Pathway

- Damage to tissue outside the vessel
- Tissue Thromboplastin

Intrinsic Pathway

- Damage to the blood vessel
- Cascade of clotting factors

- Inactive Factor X
- Activated Factor X

- Prothrombin
- Thrombin

- Fibrinogen
- Fibrin
- Blood Clot

Factor XIII

MECHANISM OF PLATELET ACTIVATION
Options available for fibrinogen replacement and what doses to give.

1. FFP

- Most widely available source of fibrinogen.
- Low and variable levels of fibrinogen.
- Long preparation and administration time.
- Has a large volume.
- Has a significant number of transfusion related complications and is of poor efficacy.

NOT RECOMMENDED AS A SOURCE OF FIBRINOGEN REPLACEMENT.
Options available for fibrinogen replacement and what doses to give.

2. CRYOPRECIPITATE

- Contains fibrinogen (approx 15g/L).
- Small volume per unit.
- Takes time to thaw.
- Significant number of transfusion related risks.
- Standard dose is 10 units.
- Increase in fibrinogen levels is very variable.
- No longer available in Europe.
Options available for fibrinogen replacement and what doses to give.

3. Fibrinogen concentrate

- Freeze dried lyophilized preparations of fibrinogen (Haemocomplettan, Riastap, Clottagen, Fibrinogen HT, Fibroraas).

- Delivers a standard amount of fibrinogen per vial (900-1400mg per vial).

- Fast reconstitution.

- Minimal transfusion related complications.

- No cross match required.

- Half life is 2.7 days.

- Given as a dose of 4-8g (4g usually increases levels by 1g/L).
RiaSTAP® is indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia.

See Package Insert for Directions.

The vial of RiaSTAP® must be reconstituted with 50 mL Water for Injections.

The vial of RiaSTAP® contains:
Fibrinogen (human) ...................... 900–1300 mg
Albumin (human) ....................... 400–700 mg
Arginine hydrochloride .............. 375–660 mg
Sodium chloride ....................... 200–350 mg
Sodium citrate ......................... 50–100 mg

Contents:
1 vial of RiaSTAP®

®Registered Trademark of CSL Limited
Group of Companies
KEEP OUT OF REACH OF CHILDREN

RiaSTAP®

Human Fibrinogen, Powder for Injection

Intravenous Injection Only

1 g

Manufactured by CSL Behring GmbH
35041 Marburg Germany

Distributed and sponsored in Australia by CSL Limited
189 - 209 Camp Road
Broadmeadows Vic 3047 Australia
Customer Service 1800 063 892
RiaSTAP®
Human Fibrinogen, Powder for Injection

Lot no. 35169911A
1 g

Expiry Date
10.2014.
Lot no. 35169911A

KEEP OUT OF REACH OF CHILDREN

Human Fibinogen
1 g

Manufactured by CSL Ltd
35041 Murrumbeena Road
Broadmeadows, Victoria
Australia

Distributed by CSL Ltd
189-191 Havelock Street
West Melbourne, Victoria
Australia
Evidence for the benefit of fibrinogen in CPB related bleeding.

- Studies have compared FFP with fibrinogen concentrate in bleeding patients.

- 18 of 20 studies showed NO reduction in blood loss in the FFP groups.

- Studies with fibrinogen concentrate have shown reduced postoperative blood loss in 60% of patients. One study after CPB 35 of 39 patients required no further products.
Evidence for the benefit of fibrinogen in CPB related bleeding.

- Studies in cardiac surgery have a significant association between FFP and reduced in hospital survival.

- Studies of fibrinogen concentrate consistently show reduced blood loss, reduced allogenic transfusion, reduced ICU and hospital length of stays and increased fibrinogen levels.

- In 5 comparator trials 70% of outcomes with fibrinogen showed a benefit over controls. In 3 studies FFP was the control providing evidence that fibrinogen concentrate is more effective than FFP.
After standard dose of 4-8g of fibrinogen both PT and APTT were significantly improved at 24 and 72 hours.

A recent pilot study has demonstrated targeting bleeding patients post CPB with fibrinogen levels in the low normal range to achieve a concentration in the upper normal range reduced bleeding.

Post CPB median fibrinogen levels fall to 1.5g/L which is borderline for adequate hemostasis. On average fibrinogen levels decrease by 34-42% during CPB.
What is an appropriate fibrinogen level to trigger treatment?

- Increasing data suggests the traditional trigger of 1g/L is too low and 1.5-2g/L is a better trigger.

- FIBTEM guidance provides a real time measure and trigger.

- Only treat if there is also ACTIVE bleeding.
Evidence for the benefit of fibrinogen in CPB related bleeding.

- Pig models of dilutional coagulopathy- fibrinogen deficiency is the first defect observed. CPB studies in humans have shown the same result.

- Patients with high fibrinogen levels have fewer bleeding complications.

- Low preoperative fibrinogen has been shown to be associated with increased postoperative blood loss.
Evidence for the benefit of fibrinogen in CPB related bleeding.

- In porcine models of uncontrolled hemorrhage fibrinogen concentrate improved clot firmness and slowed blood loss.

- Was more effective than platelets even in the presence of thrombocytopenia. (Consistent with the cellular model of coagulation).

- Some evidence that the effect of clopidogrel can be overcome by increasing fibrinogen concentration.
WHEN TO USE FIBRINOGEN CONCENTRATE

INTUITION

BLEEDING PATIENT

LOW FIBRINOGEN

GIVE FIBRINOGEN
Thromboelastometry
Using ROTEM® delta
Normal patient
ROTEM Tests

**EXTEM:** activation of clot formation by thromboplastin (tissue factor)
Assessment of:
- the factors VII, X, V, II, I
- platelets, fibrinolysis

**INTEM:** activation of clot formation via the contact phase.
Assessment of:
- the factors XII, XI, IX, VIII, X, V, II, I,
- platelets, fibrinolysis
Activation as in EXTEM with addition of cytochalasin D, a platelet-blocking substance. In the FIBTEM assay fibrinogen levels and fibrin polymerisation can be assessed in a functional way.

**EXTEM**: $MCF = \Sigma$ Fibrinogen + platelets + F XIII activity

**FIBTEM** = Normal Result of fibrinogen. No requirement for FFP, cryo-precipitate or fibrinogen. Patient 1 requires Thrombocytes.

**FIBTEM** = Abnormal result
Patient 2 requires fibrinogen, cryo-precipitate or FFP.
TPCH Cardiac Surgery ROTEM / Multiplate Transfusion Algorithm

Do not treat patient unless there is clinically significant bleeding

Pre Bypass
(treatment with high risk pts, anti-platelet therapy, pre-existing haemostatic abnormalities, etc.)

Drug History - Clopidogrel, Prasugrel, Ticagrelor, Aspirin, Fish Oil, Garlic or Ginseng, etc., within the last 7 days?

Multiplate
ADP - AUC < 30
ASPI - AUC < 20
TRAP - AUC < 50

Yes

Poor Platelet Function

Yes

Consider pre-ordering platelets for possible transfusion post CPSI

Tranexamic Acid

On Bypass (30 minutes before coming off bypass)

FIBTEM - MCF < 5mm

Yes

Low Fibrinogen

Yes

Consider Cryoprecipitate Availability

ExTEM A10 < 30mm

Yes

Poor Platelet Contribution

Yes

Consider Platelet Availability

Post Bypass (10 post protamine)

INTEM - CT > 240 secs
HEPTEM - CT / INTEM - CT < 0.8

Yes

Heparin Effect

Yes

Redosage of Protamine

ExTEM A10 < 40mm
FIBTEM A10 < 10mm

Yes

Low Fibrinogen

Yes

Cryoprecipitate

ExTEM - CT > 90 secs
HEPTEM - CT > 280 secs

Yes

Low Coagulation Factors

Yes

PCC / FFP

ExTEM A10 < 40mm

Yes

Poor Platelet Contribution

Yes

Platelets

FIBTEM A10 > 10mm

Yes

ADP - AUC < 30
ASPI - AUC < 20
TRAP - AUC < 50

Yes

Platelet Dysfunction

Yes

Hyperfibrinolysis

Yes

Tranexamic Acid

Ongoing Bleeding

Optimise

ExTEM - CT < 80 secs AND
A10 FIBTEM > 10mm - AND
A10 ExTEM > 50mm

Consider surgical haemostasis

Version 3

1/12/13
**EXTEM & INTEM**:  
- Normal CT  
- Low amplitude

**FIBTEM**:  
- Low amplitude  
=> Low fibrinogen

Low amplitude seen in **INTEM & EXTEM**  
due to fibringen deficiency

**APTEM ≈ EXTEM**

=> No hyperfibrinolysis
### Preproduct

#### Rotem Analyser, Tem Innovations

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The risks and side effects of fibrinogen therapy.

- Thromboembolic complications.

- Risk of thromboembolism from monitoring data appears low but until large trials are conducted this remains a real concern.

- Infection, immune mediated injuries, acute lung injury, and volume overload are much reduced compared with other sources of fibrinogen.
CONCLUSIONS

- Central role in hemostatic process.
- Levels drop quickly in CPB.
- Easy to measure with point of care testing.
- Data suggests it works!!!!!!
- Seems to have good safety profile.
### EXTEM

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