Fibrinogen and Bleeding

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Director, Perioperative Blood Management Services
Objectives

1. Review the role of FIBRINOGEN in hemostasis.
2. Evaluate the sources of exogenous FIBRINOGEN.
3. Assess the potential of FIBRINOGEN concentrate as a replacement for cryoprecipitate.
This talk will discuss the “off-label” use of a “special access” drug.
The PBMP has received “Unrestricted Educational Grants” from CSL Behring.
Currently in discussions with CSL Behring wrt a clinical trial using Haemocomplettan P.
Fibrinogen: What does it do?

A plasma protein critical to hemostasis (stopping bleeding) and clot formation.

Blood plasma concentrations range between 1.5 and 4.0 g/L.

Fibrinogen plays roles in both cellular and fluid phases of coagulation.
Clot Formation
RBCs trapped in Fibrin Mesh
Major Bleeding

Clotting factors and FIBRINOGEN are lost with major blood loss.

Subsequent volume replacement results in further “dilutional coagulopathy”.

FIBRINOGEN is the first clotting factor to decrease to critically low levels.

Very important to maintain FIBRINOGEN levels, especially with THROMBOCYTOPENIA.
Hemorrhage Resuscitation

Historically, hemorrhage treated with WHOLE BLOOD.
All products now fractionated.
Concentrates of RBC and Platelets do not contain enough plasma to maintain balance.
FIBRINOGEN Replacement

Three major sources of FIBRINOGEN:

- Fresh frozen plasma (FFP)
- Cryoprecipitate (Cryo)
- Fibrinogen concentrate (Haemocomplettan P)
FFP

- Contains all proteins present in human plasma.
- Used for factor supplementation during acute bleeding.
- Used in Massive Transfusion Protocols – but - risk of pathogen transmission and other reactions.
- Contains about 2 g/L of FIBRINOGEN. Therefore, requires large volumes to supplement.
Cryoprecipitate

- Human plasma concentrate first described in 1960s.
- Manufactured by thawing, then centrifuging FFP.
- Each unit is between 10-20 mls.
- “Pooled” in batches of 10 units per dose.
- Contains about 10 g/L of FIBRINOGEN.
- Exposes patients to multiple donors.
- Must be thawed and type matched prior to use.
Cryoprecipitate
Fibrinogen Concentrate

- Derived from human plasma, stored at room temperature as a pasteurized lyophilized powder.
- Does not require matching.
- Reconstituted up to 20 g/L
- Can infuse 6 g in 1 to 2 minutes.
- Risk of viral infection significantly reduced b/c of viral inactivation and removal process.
Fibrinogen Concentrate

Limited info re thrombotic potential of FIBRINOGEN concentrate.
Animal studies, and use in patients with hypofibrinogenemia demonstrated no thrombotic complications.
Uncertain re correct and appropriate administration in the critical care setting.
Fibrinogen Concentrate

- Standardized content
- Faster reconstitution
- Improved efficacy
- Significantly ↓ risk of viral transmission and immune mediated reactions
- Does not need “matching”
- Cost is about the same.
## FFP vs. Cryo vs. Fibrinogen

<table>
<thead>
<tr>
<th>Fibrinogen replacement therapies</th>
<th>Fresh frozen plasma (FFP)</th>
<th>Cryoprecipitate (Cryo)</th>
<th>RiaSTAP®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen content per unit volume</td>
<td>~500 mg per 250 mL</td>
<td>≥150 mg per 15 mL</td>
<td>~1000 mg per 50 mL</td>
</tr>
<tr>
<td>Fibrinogen content per mL</td>
<td>~2 mg per mL</td>
<td>≥10 mg per mL</td>
<td>~20 mg per mL</td>
</tr>
<tr>
<td>Exact fibrinogen content per unit</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Labeled</td>
</tr>
<tr>
<td>Thawing required</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ABO matching required</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Virus inactivation/removal</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Shelf life</td>
<td>12 months</td>
<td>12 months</td>
<td>30 months</td>
</tr>
</tbody>
</table>

Department of Anesthesia

Dalhousie University

Inspiring Minds
Faculty of Medicine
Fibrinogen

- A high ratio of fibrinogen : RBC transfusion has been associated with a reduction of mortality in combat trauma.¹

- High fibrinogen levels (> 3 g/L) may compensate for low platelet counts.²

Fibrinogen Levels

“Normal” reported by many labs to be $> 1 \text{gm/L}$
Many studies show that is insufficient.
May require $> 2.5 \text{gm/L}$ in the setting of hemorrhage.
Supplementation of FIBRINOGEN may help restore balance.
Prophylactic Fibrinogen

Pilot study showed a 32% reduction in bleeding in cardiac patients who received 2 gm pre-operatively without increased thrombosis.\(^1\)

European guidelines now recommending FIBRINOGEN in the treatment of trauma related hemorrhage

Fibrinogen Levels

Minimum fibrinogen levels for adequate hemostasis in a variety of surgeries.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Fibrinogen Level (g/l)</th>
<th>Surgery/Conditions (Time Point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerlach et al.</td>
<td>2002</td>
<td>&gt; 1.5</td>
<td>Neurosurgery (after surgery)</td>
</tr>
<tr>
<td>Charbit et al.</td>
<td>2007</td>
<td>&gt; 2.0</td>
<td>Postpartum hemorrhage</td>
</tr>
<tr>
<td>Bolliger et al.</td>
<td>2009</td>
<td>&gt; 2.0</td>
<td>CABG on-pump and off-pump (after surgery)</td>
</tr>
<tr>
<td>Bolliger et al.</td>
<td>2009</td>
<td>2–3</td>
<td>In vitro hemodilution</td>
</tr>
<tr>
<td>Fenger-Eriksen et al.</td>
<td>2010</td>
<td>2.4</td>
<td>Cystectomy (after surgery)</td>
</tr>
<tr>
<td>Blome et al.</td>
<td>2005</td>
<td>2.7</td>
<td>CABG on-pump (after surgery)</td>
</tr>
<tr>
<td>Karlsson et al.</td>
<td>2009</td>
<td>3.1</td>
<td>CABG on-pump (after surgery)</td>
</tr>
<tr>
<td>Rahe-Meyer et al.</td>
<td>2009</td>
<td>3.6</td>
<td>Replacement of ascending aorta (after surgery)</td>
</tr>
</tbody>
</table>

Fibrinogen levels are the cutoff levels in retrospective studies, the optimal level in the in vitro study, and the levels in the interventional groups of placebo-controlled studies.

CABG = coronary artery bypass grafting.

Bolliger D. et al. Anesthesiology. Nov 2010
Clinical Study

Several small, retrospective studies (historical controls).

TAAA Study: 18 Patients (12 control and 6 study) underwent TAAA surgery.

Sixty-six percent of patients in the FIB group received NO blood products in the first 24 hours.
Fibrinogen and ROTEM

Before therapy

<table>
<thead>
<tr>
<th>mm</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>min</th>
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<tbody>
<tr>
<td>68</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>20</td>
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<td>40</td>
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</table>

MCF = 48 mm

A

After therapy

<table>
<thead>
<tr>
<th>mm</th>
<th>10</th>
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<td>40</td>
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</table>

MCF = 58 mm

<table>
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<th>mm</th>
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<th>40</th>
<th>50</th>
<th>min</th>
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<tr>
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<td>60</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

MCF = 22 mm

B * Reference range: 50–72 mm

** Reference range: 9–25 mm
CDHA Fibrinogen Study

Dr. Myron Kwapisz (PI)
Dr. Blaine Kent (Co-I)

Support via Departments of Anesthesia and Cardiac Surgery, CDHA grant, CSL Behring.

Prospective, double blind, randomized control trial in “high risk” cardiac surgery.

Will be recruiting soon.
Treatment Paradigm

Hemophilia used to be treated with Cryo, but now only with specific factors for SAFETY reasons.

Why are we using Cryo for bleeding when a safer concentrate is available.
Conclusions

Fibrinogen Concentrates may:

- Reduce blood loss
- Decrease the need for other components such as RBC / FFP / Platelets
- Restore
- Coagulation
- Improve survival
References


