The Composition and Use of Plasma Components

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for the

Clinical Transfusion Medicine Committee
AABB

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What is “FFP”? What is “FFP”?

WHOLE BLOOD

1 Unit RBC

Centrifuge

Platelet-Rich Plasma (PRP)

1 Unit Plasma

Freeze, Thaw, Centrifuge

1 Unit Platelets

1 Unit cryoprecipitate + 1 Unit plasma (Cryoprecipitate-Reduced)

1 Unit (~250 mL) Fresh Frozen Plasma

Freeze within 8 hr*

Plasma can also be frozen after 8h but before 24h
What About FFP Made from Apheresis Collections?

Volume: 200 – 600 mL

Content: Plasma Anticoagulant

200 mL
250 mL
300 mL
500 mL
600 mL
Handling Options for FFP

- **FFP**
  - Stored frozen colder than -18°C

- **FFP, Thawed**
  - Thawed at 30-37°C
  - 4°C
  - >24 h

- **Thawed Plasma**

(to 5 d after thawing)
## Coagulation Factor Activity of Thawed Plasma

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>% change Day 1 to 5</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibr</td>
<td>225</td>
<td>224</td>
<td>224</td>
<td>224</td>
<td>225</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>II</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>80</td>
<td>80</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>V</td>
<td>79</td>
<td>75</td>
<td>71</td>
<td>68</td>
<td>66</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>VII</td>
<td>90</td>
<td>81</td>
<td>76</td>
<td>72</td>
<td>72</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>VIII</td>
<td>107</td>
<td>76</td>
<td>66</td>
<td>65</td>
<td>65</td>
<td>41</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>X</td>
<td>85</td>
<td>84</td>
<td>84</td>
<td>82</td>
<td>80</td>
<td>6</td>
<td>NS</td>
</tr>
</tbody>
</table>

(Tabular entries as % activity.)

Downes K et al. *Transfusion* 2001;41:570.
The Challenge of Frozen Plasma Usage

A readily available source of procoagulants that can be life saving for patients in need of hemostatic assistance. But there is lack of consensus around definition of the circumstances when this component will truly benefit a patient.
Abnormalities in Coagulation Testing do not necessarily indicate a Clinical Coagulopathy

<table>
<thead>
<tr>
<th>Procoagulant</th>
<th>Consumed in Coagulation?</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>Yes</td>
<td>Normal: 200-400 mg/dL</td>
</tr>
<tr>
<td>Factor V</td>
<td>Yes</td>
<td>Hemostatic: 50-100 mg/dL</td>
</tr>
<tr>
<td>Factor VII</td>
<td>No</td>
<td>Normal: 1 U/mL</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Yes</td>
<td>Hemostatic: 5-25%</td>
</tr>
</tbody>
</table>

Normal concentration: 1 U/mL = 100% activity
Clinical Indications for Plasma

- **Bleeding** with deficiency of multiple coagulation factors
- **Bleeding** with specific factor deficiency, no concentrate available
- Pre-op setting with deficiency of multiple coagulation factors
- Pre-op setting with specific factor deficiency, no concentrate available
- Massive transfusion with coagulation abnormalities
- **Bleeding or urgent invasive procedure** while on warfarin therapy
- Thrombotic thrombocytopenic purpura (TTP)
- Rare specific plasma protein deficiencies, e.g., C1-esterase inhibitor

Using Screening Tests to Predict Plasma Need

Mild elevations of PT or aPTT overestimate clinical benefit of transfusing FFP for patients in most clinical situations.

Recommended transfusion trigger points in appropriate situations:
- 1.3 x upper limit of reference range (in seconds)
- or –
- 1.5 x midpoint of reference range (in seconds)

NOT INR=1.5

Auble T et al. Acad Emerg Med 2002;567-574
Using Screening Tests to Predict Plasma Need

Patients experiencing massive transfusion after trauma

Patients with Generalized Bleeding


<table>
<thead>
<tr>
<th>Test</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td></td>
</tr>
<tr>
<td>&lt;1.3</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;1.3</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>75%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
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</tr>
</thead>
<tbody>
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<td></td>
</tr>
<tr>
<td>&lt;1.3</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;1.3</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>75%</td>
</tr>
</tbody>
</table>
Using Screening Tests to Predict Plasma Need

Effect of plasma dilution on procoagulants

- Factor VIII
- Factor X
- Fibrinogen
- PT
- PTT

% Remaining (log scale)

Plasma Removed (mL)

## Using Screening Tests to Predict Plasma Need

### Patients undergoing percutaneous liver needle biopsy

<table>
<thead>
<tr>
<th>Test</th>
<th>Group</th>
<th>n</th>
<th>Bleeding Complications</th>
<th>Hb Change (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>Normal</td>
<td>100</td>
<td>4%</td>
<td>-0.3±0.9</td>
</tr>
<tr>
<td></td>
<td>1.3 x ULN</td>
<td>43</td>
<td>6%</td>
<td>-0.2±0.8</td>
</tr>
<tr>
<td>PTT</td>
<td>Normal</td>
<td>103</td>
<td>5%</td>
<td>-0.3±0.9</td>
</tr>
<tr>
<td></td>
<td>1.3 x ULN</td>
<td>34</td>
<td>3%</td>
<td>-0.1±0.6</td>
</tr>
</tbody>
</table>

ULN = Upper limit of normal  
(No pre-biopsy FFP prophylaxis given.)

Best predictor of bleeding was a finding of malignancy in the biopsy.

Using Screening Tests to Predict Plasma Need

Patients undergoing laparoscopic liver needle biopsy


Note: 10% change in activity = approximately 1 sec
Predicting Plasma Need
Effect of coumadin therapy on perioperative blood loss

### Predicting Plasma Need

*Effect of coumadin therapy on post-operative blood loss*

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Post-Op Blood Loss (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>26</td>
<td>813 (125-2125)</td>
</tr>
<tr>
<td>Therapeutic coumadinization</td>
<td>26</td>
<td>624 (210-1650)</td>
</tr>
</tbody>
</table>

Procedure: Mitral commissurotomy

## Indices Predictive of Microvascular Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>89%</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td>1.8</td>
<td>44%</td>
<td>96%</td>
<td>80%</td>
</tr>
<tr>
<td>PTT ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>56%</td>
<td>56%</td>
<td>26%</td>
</tr>
<tr>
<td>1.8</td>
<td>56%</td>
<td>96%</td>
<td>83%</td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50,000/mL or</td>
<td>89%</td>
<td>93%</td>
<td>73%</td>
</tr>
<tr>
<td>Fibrinogen &lt; 50 mg/dL</td>
<td></td>
<td></td>
<td>96%</td>
</tr>
</tbody>
</table>

PT ratio = Patient’s PT (sec) / midpoint (sec) of PT reference range
PTT ratio = Patient’s PTT (sec) / midpoint (sec) of PTT reference range

An Analysis of the Literature

Normal vs. Abnormal Coagulation Tests

Angiography
Angiography
Bronchoscopy
Liver biopsy
Liver biopsy
Liver laparoscopy
Liver laparoscopy
Transjugular liver biopsy
Transjugular liver biopsy
Transjugular liver biopsy
Para/thoracentesis
Transjugular kidney biopsy
Kidney biopsy

## Predicting Bleeding

*By bleeding score and service*

<table>
<thead>
<tr>
<th>Score</th>
<th>Medical</th>
<th>Surgical</th>
<th>Trauma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/37</td>
<td>1/320 (0.3%)</td>
<td>0/42</td>
<td>1/299 (&lt;1%)</td>
</tr>
<tr>
<td>3-7</td>
<td>7/77 (9%)</td>
<td>2/194 (1%)</td>
<td>1/84 (1%)</td>
<td>10/355 (&lt;3%)</td>
</tr>
<tr>
<td>≥8</td>
<td>4/8 (50%)</td>
<td>0/4</td>
<td>1/11 (9%)</td>
<td>5/23 (22%)</td>
</tr>
<tr>
<td>Total</td>
<td>11/122 (9%)</td>
<td>3/518 (0.6%)</td>
<td>2/137 (1.4%)</td>
<td>16/777 (2%)</td>
</tr>
</tbody>
</table>

### Score calculation

3 points for each of the following:
- PT 18-24 seconds, PTT 48-64 seconds, Platelet Count 20-49,000/microL, serum creatinine > 1.4

4 points for each of the following:
- PT >24 seconds, PTT >64 seconds, Platelet Count <20,000/microL

Bleeding Prediction Score = sum of points

DeLoughery TG *et al.* *Transfusion* 1996;36:827-31
Intra-Op Assessment: The Thromboelastogram
Correcting Over-Coumadinization

**Clinical Significance**
- INR >8 due to coumadin → Major bleeding in 12/77 (13%)
- Two fatalities (3%) without FFP or vitamin K treatment

**Correction with FFP**
- REVERSAL ALMOST *IMMEDIATE* BUT NOT NECESSARILY LASTING
- FFP transfusion → INR = 2.3 (1.6-3.8)

**Correction with Vitamin K**
- REVERSAL IN 6-12h
- Administration: oral, subcutaneous or IV (more rapid action)
- Dose may be repeated, as necessary.

Murphy PT et al. *Clin Lab Haematol* 1998;20:253-7
## Correcting Over-Coumadinization

**Recommendations of American College of Chest Physicians**

<table>
<thead>
<tr>
<th>CLINICAL SITUATION</th>
<th>GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &gt; therapeutic range but &lt; 5.0; no significant bleeding</td>
<td>Lower the dose; or omit the next dose, and resume therapy at a lower dose when the INR is within therapeutic range; if the INR is only slightly above therapeutic range, dose reduction may not be necessary. Alternatively, omit a dose and give vitamin K₁ (1 to 2.5 mg orally), especially if the patient is at increased risk for bleeding. Patients requiring more rapid reversal before urgent surgery: vitamin K₁ (2 to 4 mg orally); if INR remains high at 24 h: an additional dose of vitamin K₁ (1 to 2 mg orally).</td>
</tr>
<tr>
<td>INR &gt; 5.0 but &lt; 9.0; no significant bleeding</td>
<td>Omit the next dose or two, monitor INR more frequently, and resume therapy at a lower dose when the INR is within therapeutic range.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL SITUATION</th>
<th>GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &gt; 9.0; no significant bleeding</td>
<td>Omit warfarin; give vitamin K₁ (3 to 5 mg orally); closely monitor the INR; if the INR is not substantially reduced in 24 to 48 h, monitor the INR more often, giving additional vitamin K₁, if necessary. Resume therapy at a lower dose when the INR is within therapeutic range.</td>
</tr>
</tbody>
</table>

| INR > 20; serious bleeding | Omit warfarin; give vitamin K₁ (10 mg, slow IV infusion), supplemented with fresh plasma or prothrombin complex concentrate, depending on urgency; vitamin K₁ injections can be repeated every 12 h. |

| Life-threatening bleeding | Omit warfarin; give prothrombin complex concentrate with vitamin K₁ (10 mg by slow IV infusion): repeat if necessary, depending on the INR. |

Ansell J et al. Chest 2004;126(3Suppl):204S-233S.
Plasma Dosage

**USUAL DOSE FOR CONTROL OF BLEEDING:** 10-20 mL/kg

**Determineants**

- Patient size
- Bleeding site
- Factor activity: Initial, target
- Factor concentration in plasma and recovery
- Factor half-life in vivo
- Unit volume

**Rx:** 2 units??

PLASMA

**PLASMA**
Procoagulant Recovery and Survival

70 kg patient with 3000 mL plasma volume receiving FFP (20 mL/kg)

ASSUMPTIONS:
Stable plasma volume after expansion
85% procoagulant activity in plasma
100% recovery

Synthetic capacity to maintain pre-transfusion procoagulant activity

Fibrinogen ($t_{1/2} = 3^d$)
Factor X ($t_{1/2} = 20h$)
Factor VIII ($t_{1/2} = 12h$)
Factor VII ($t_{1/2} = 5h$)
Considerations in Massive Hemorrhage

Surgical bleeding vs. coagulopathic bleeding?

Adequacy of resuscitation?

Extent of hypothermia and acidosis?

Effect of Body Temperature on Coagulation

Effect of Acid/Base Balance on Coagulant Activity

# Cumulative Effects of Hypotension and Hypothermia

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Conditional Probability of Developing Coagulopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk Factor</td>
<td>1%</td>
</tr>
<tr>
<td>Severe trauma*</td>
<td>10%</td>
</tr>
<tr>
<td>+Systolic BP &lt; 70mm Hg</td>
<td>39%</td>
</tr>
<tr>
<td>+pH &lt; 7.1</td>
<td>49%</td>
</tr>
<tr>
<td>Severe trauma + Temp &lt; 34°C</td>
<td>49%</td>
</tr>
<tr>
<td>+Systolic BP &lt; 70mm Hg</td>
<td>85%</td>
</tr>
<tr>
<td>+pH &lt; 7.1</td>
<td>98%</td>
</tr>
</tbody>
</table>

*Injury severity score of >25.

Stored frozen colder than -18°C

Thawed at 4°C, then centrifuged

Cryo-reduced Plasma

- Derivatives
- TTP exchange

Cryo

Cryoprecipitate

Factor VIII (> 80 U)
vWF
Fibrinogen (~200 mg)
Indications for Cryoprecipitate

Clinically significant deficiency of

Fibrinogen

*Factor VIII*

von Willebrand Factor*

*Use of a commercial, viral inactivated clotting factor concentrate may be preferable
Adverse Effects of Plasma Transfusion

- Allergic reaction
- Anaphylaxis
- Volume overload
- Transfusion-related acute lung injury (TRALI)
- Viral infections (HIV, HBV, HCV)
- Others