Role of Plasma in Massive Hemorrhage

Shuoyan Ning, MD FRCPC
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Objectives

• Role of ratio-based plasma to red cell transfusion
• Group A plasma
• Plasma alternatives
Disclosures

• None
Case

• 28 year old man suffered motorcycle collision
• Presented to your hospital as a transfer from another hospital due to hemodynamic instability and need for trauma care
• Patient required CPR, intubation, 7 units of Group O+ Red Blood Cells (RBCS) and 1 unit of Group AB Frozen Plasma (FP)
• On arrival, he is requiring ongoing vasopressor support and has bilateral pneumothorax, significant intra-abdominal collections and a long bone fracture of his femur.
• Labs are drawn and pending
• Massive transfusion protocol is started
Question 1

What is the optimal initial FP:RBC ratio for him in the massive transfusion protocol?

A. 1 to 1  
B. 1 to 2  
C. 2 to 1  
D. 1 to 3
Definition of Massive Hemorrhage

• No widely accepted universal definition
  – Loss of 1 blood volume in 24 hours
  – 50% loss of 1 blood volume in 3 hours
  – Blood loss of > 150ml/min
  – >10 units of RBCs in 24 hours, 6 units of RBCs in 4 hours etc.
  – Anticipated blood loss ≥10 units of RBCs within 6 hours
  – Clinical parameters – hypotension, tachycardia

• Complex and stressful medical situations

• High mortality

Acute Coagulopathy of Trauma

Coagulopathy of Trauma

• Coagulopathy is common in trauma and associated with increased mortality
• Observational cohort study of 1088 trauma patients
  – Coagulopathy: PT > 18s, aPTT > 60s, or TT > 15s
  – 24% of patients were coagulopathic on arrival
  – Incidence of coagulopathy increased with the severity of injury
  – Patients with coagulopathy had higher mortality (46% vs 10.9%, p<0.001)

Brohi K et al., J Trauma 2003 Jun;54(6):1127-30.
680 patients with major bleeding from severe trauma randomized to FP:PLT:RBC of 1:1:1 versus 1:1:2
Mortality at 24h and d30 not different (Primary outcome)
1:1:1 more likely to have adequate hemostasis (86% versus 78%) and had fewer deaths from exanguination at 24 hours (9.2% versus 14.6%)
No differences in 23 other ancillary clinical outcomes

Optimal Dose, Timing and Ratio of Blood Products in Massive Transfusion: Results from a Systematic Review

Zoe K. McQuilten a,b,*, Gemma Crichton a, Susan Brunskill c, Jessica K. Morison a, Tania H. Richter a, Neil Waters a, Michael F. Murphy c, Erica M. Wood a

- 6 RCTs (5 adult trauma, 1 pediatric burn), 10 RCTs ongoing
- 3/6 (2 adult trauma, 1 pediatric burn) investigated effect of FP:RBC ratio on patient outcomes
- Data from the 2 trauma trials were pooled for meta-analysis of 28d mortality
- Higher FP:RBC ratios associated with more FP use, without significant difference in morbidity/mortality (pooled effect measure for 28d mortality 1.26, 95% CI 0.49-3.22, p=0.64, I²=75%)
- **Insufficient evidence to recommend 1:1 (FP:RBC) over 1:2 (FP:RBC)**

Non Trauma Massive Hemorrhage

**Obstetrics**
- 25% of cases of OB hemorrhage is associated with coagulopathy
- Fibrinogen is key
  - Low levels are a predictor of PPH severity (normal 4-6 g/L in pregnancy)
  - Fibrinogen replacement and TXA (WOMAN trial) are key

**GI bleeding**
- Less coagulopathy
- ~5% of cases require FP transfusion (TRIGGER trial)

**Cardiac surgery**
- Coagulopathy different – secondary to bypass mediated platelet activation and factor consumption

**Liver surgery**
- Coagulopathy different – balance of lack of clotting factors and lack of natural anticoagulants
- Have intact thrombin generating capacity and have hypo-fibrinolytic state

Charbit B et al., JTH 2006
Pavord S et al. Blood 2015
Hunt B et al. BJH 2015.
Myles P et al. NEJM 2017

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Non Trauma Massive Hemorrhage

**Obstetrics**
- 25% of cases of OB hemorrhage is associated with coagulopathy
- Fibrinogen is key
  - Low levels are a predictor of PPH severity (normal 4-6 g/L in pregnancy)
  - PPV of fibrinogen < 2g/L for PPH was 100%
  - Fibrinogen replacement and TXA (WOMAN trial) are key

**GI bleeding**
- Less coagulopathy
- ~ 95% of cases require RBC transfusions only (TRIGGER trial)

**Cardiac surgery**
- Coagulopathy different – secondary to bypass mediated platelet activation and factor consumption

**Liver surgery**
- Coagulopathy different – balance of lack of clotting factors and lack of natural anticoagulants
- Have intact thrombin generation capacity and have hypo-fibrinolytic state

Charbit B et al., JTH 2006
Pavord S et al. Blood 2015
Hunt B et al. BJH 2015.
Myles P et al. NEJM 2017
FP:RBC Ratios in Non-Traumatic MH

• Etchell et al. Critical Care Med 2017
  – Retrospective single-center study of 601 massively bleeding non-trauma patients
  – Primary outcome: 30 day mortality
• Cardiac Sx, GI, hepato-biliary bleeds were most common
• Higher FP:RBC ratios (> 1:2) was NOT associated with increased 30-day mortality

Etchell E et al. Critic Care Med 2017; Aug;45(8)
FP:RBC Ratios in Non-Traumatic MH

- Retrospective study of 865 massive transfusion events in a single academic center

![Figure. Adjusted Odds Ratio (OR) for Death](image)

<table>
<thead>
<tr>
<th>Surgical Service</th>
<th>No. of Patients</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular surgery</td>
<td>78</td>
<td>0.16 (0.03-0.79)</td>
</tr>
<tr>
<td>Medicine</td>
<td>76</td>
<td>8.48 (1.50-47.75)</td>
</tr>
<tr>
<td>Trauma surgery</td>
<td>99</td>
<td>0.63 (0.17-2.35)</td>
</tr>
<tr>
<td>General surgery</td>
<td>86</td>
<td>4.27 (1.28-14.22)</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>272</td>
<td>0.98 (0.45-2.14)</td>
</tr>
<tr>
<td>All patients without trauma</td>
<td>767</td>
<td>1.10 (0.72-1.70)</td>
</tr>
</tbody>
</table>

Overall, no benefit was observed for high or low fresh frozen plasma (FFP) to red blood cells (RBC) ratio. In vascular surgery, a high FFP:RBC ratio was associated with a survival benefit. In medicine and general surgery, a high FFP:RBC ratio was associated with increased mortality.

Mesar T et al. JAMA Surg 2017 Jun 1;152(6):574-580
Ratio vs Lab-Driven Plasma Transfusion

- Fixed-ratio based = continuing with pre-set transfusion ratio until bleeding stops/protocol deactivated/death
- Lab-based = transfusing based on lab results instead of empiric ratios
- Ratio-based increases in plasma wastage
- Starting with fixed-ratio → lab directed
  - Routine coagulation tests (INR, aPTT, fibrinogen)
    - INR<1.8
    - Fibrinogen>1.5 g/L
  - Point of care whole blood clotting assays (TEG®, ROTEM®)

Hunt B et al. BJH 2015
Nascimento B et al. CMAJ 2013
Tapia N et al. J Trauma Acute Care Surg 2013
28M traumatic massive hemorrhage → what is the best FP:RBC ratio for him?

- No established benefit to a 1:1 transfusion ratio of FP:RBC, and associated with more plasma use
- Therefore, a target of ~1:2 (FP:RBC) is likely sufficient until labs or point of care tests are available to guide further therapy
Case

- Patient taken to OR
- 40 units of O+ RBCs
- 7 doses of platelets
- 24 units of Group AB plasma
- 12g of fibrinogen concentrate
- G/S just drawn, pending
It’s Friday heading into a long weekend and we will have NO more AB plasma if this keeps up! What should we DO?
Question 2

Running out of AB plasma stock

A. Continue with AB plasma, until G/S back
B. Switch to A plasma, until G/S back
C. Switch to O plasma, until G/S back
D. Stop plasma transfusions for awaiting G/S
AB Plasma

• AB plasma is an universal product
• A limited resource (3-4% of the population is group AB)
• Multinational survey BEST: 73% of AB plasma is transfused to non-AB patients
  – Highest % occurred in ER
  – Most common indication was emergency issue to patients without valid G/S (69%)
  – Group AB plasma close to expiry (16.4%)
• Survey of 10 US blood centers: 27% increase in demand for AB plasma in 2011 when compared to 2006
  – Widespread adoption of massive transfusion protocols

Emergency issue
Massive transfusion protocols

Data courtesy of Dr. Michelle Zeller
Can we use Group A plasma instead?

- Group A plasma contains anti-B antibodies
- If given to group B or group AB patient
  - Acute hemolytic transfusion reaction
  - Other adverse events: activate complement cascade, DIC, acute renal failure etc.

- >80% of the population is Group A or O
- Transfused anti-B will be diluted in much larger plasma volume
- Patients are receiving O RBCs
- Most B and AB patients are secretors – with free floating B antigens in their plasma to neutralize the anti-B

| Percentages of Blood Groups in Canada (%) |
|---|---|---|---|
| O  | A  | B  | AB |
| 46 | 42 | 9  | 3  |

Isaack et al. Immunohematology 2011;27:61-65
Can we use Group A plasma instead?

• We transfuse platelets containing non-identical plasma but hemolytic reactions are rare

• Cold stored, low-titer, Group O whole blood to trauma patients of unknown ABO type not associated with hemolysis or renal failure among non-group O patients

Mair B et al. Transfusion 1998;38:51-5
Berseus et al. Transfusion. 2013 Jan;53 Suppl 1:114S-123S
Seheult et al. Transfus Med 2017;27:30-5
Yazer et al. Transfusion. 2018 Feb;58(2):532-538
Are there any alternatives for transfusion of AB plasma as universal donor in an emergency release setting?

Kirsten Balvers,¹,² Sarah Saleh,¹,² Sacha S. Zeerleder,³,⁴ J. Henriette Klinkspoorn,⁵ J. Carel Goslings,¹ and Nicole P. Juffermans²

• **Systematic review** identified 6 studies (5 retrospective cohort, 1 sub-study of RCT)
• 4/6 compared ABO compatible with incompatible plasma in emergency issue
  – **No differences** in complications or mortality between transfusion of ABO compatible and ABO incompatible plasma
• 2/6 compared ABO identical with ABO compatible plasma
  – Associated increased incidence of lung injury and mortality (odds ratio, 1.10; 95% confidence interval, 1.04-1.15, p = 0.0003)
Safety of the use of group A plasma in trauma: the STAT study

Nancy M. Dunbar¹ and Mark H. Yazer,² on behalf of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative and the STAT Study Investigators†

• Multicenter retrospective observational study of 17 trauma centers using group A plasma for patients of unknown ABO group

• Group A VS Group B or AB patients who received ≥ 1 unit of A plasma

• Primary outcome: in-hospital mortality
354 group B or AB trauma patients vs 809 group A trauma patients

For group B/AB patients, mean 4 units of group A FP (range 1-58)

76% of participating centers did not measure anti-B titers

No reported acute hemolytic transfusion reactions

<table>
<thead>
<tr>
<th>TABLE 3. Outcome data between groups*</th>
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<tr>
<td></td>
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<tr>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Survival to discharge</td>
</tr>
<tr>
<td>In-hospital death</td>
</tr>
<tr>
<td>Early mortality (&lt;24 hr)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
</tr>
</tbody>
</table>

* Categorical data are reported as number (%), and continuous data are reported as mean (range, SD).
Case

- 28M traumatic massive hemorrhage $\rightarrow$ ++ AB plasma

- GET THAT GROUP AND SCREEN!!!

- Reasonable to consider switching to group A plasma
Plasma Alternatives

• **Prothrombin Complex Concentrate (PCC)**
  – Human plasma derived product with Factor II, VII, IX, X (and protein C, S, heparin)
  – Reversal of VKA
  – Reversal of direct oral anticoagulants (Apixaban, Rivaroxaban, Edoxaban)
    • 50IU/kg
    • 2000IU

<table>
<thead>
<tr>
<th>Dose</th>
<th>INR &lt; 3</th>
<th>INR 3-5</th>
<th>INR &gt; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000IU</td>
<td>2000IU</td>
<td>3000IU</td>
<td></td>
</tr>
</tbody>
</table>

Plasma Alternatives

• PCCs can be used as an alternative for plasma in massively bleeding patients when plasma is not available

• **RETIC trial** Lancet Hematology 2017
  – Single center, parallel-group, open label RCT
  – Adult patients with bleeding and coagulopathy (defined by ROTEM) randomized to:
    – FP VS clotting factor concentrate (primarily fibrinogen concentrate or 4 factor PCC)
    – Study was terminated early for futility and safety after 100 patients enrolled

• Increased thrombin generation over days

Plasma Alternatives

• Freeze-dried/lyophilized plasma
  – France, Germany, South Africa
  – FDA grants emergency use freeze dried plasma (France) to US Department of Defense in July 2018
  – French and German products in trials of trauma and pre-hospital settings
  – US products in phase 1 clinical trials

Conclusions

• Plasma is an important component of transfusion therapy in massively bleeding patients
• Empiric ratio > 1:2 (FP:RBC) may not be necessary in trauma and non-trauma patients with massive bleeding
• Group A plasma is likely a reasonable alternative to AB plasma
• More data needed for PCCs and lyophilized plasma