An Update on the Transfusion Management of Massively Bleeding Patients

Philippine Association of Medical Technologists
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Disclosure

None of the planners, staff or faculty for this course has any relevant financial relationships with commercial interests.
Objectives

Upon completion of this exercise participant should be able to:

• Define what is a massive transfusion;
• Describe the main problems of massively bleeding patients;
• Summarize findings from the most important, recent literature;
• Review recent advances in the transfusion and adjunct management of massively bleeding patients, such as:
  o Pre-hospital management,
  o Obstetrical management, and
  o The use of group A “bridging/universal” plasma;
• Distinguish between massive transfusion protocols and emergency release protocols;
• Describe the American College of Surgeons’ current recommendations for managing massive transfusions
This continuing education exercise covers topics where health disparity may exist with respect to patient diagnosis, condition, and/or treatment relevant to:

- Age
- Ethnicity
- Sexual Orientation
- Physical Abilities
- Gender
- Race
- Religious Beliefs
- Other CLC Attributes (Specify)
Outline

• Definitions & Background
• Literature Review
• Management Recommendations
• Take-Home Messages
• Knowledge Assessment
• Q & A
Massive Transfusion Update

Definitions & Background
Massive Transfusion Definitions

- **Primary Definition**: Transfusion to adult of \( \geq 8 \text{-to-10 RBC units (i.e., } \sim 1.0 \text{ total blood volume)} \) in \( \leq 24 \text{ hours} \)

- **Other Definitions** (suggestive for incipient loss of one full blood volume):
  - \( \sim 4 - 5 \text{ RBC units given to adult in } \leq 4 \text{ hours} \) (with continued major bleeding)
  - Continuing blood loss exceeding 150 ml/min

Background: Clinical Situations Most Commonly Warranting Massive Transfusions

- Trauma
- Obstetrics
- Surgery (e.g., cardiothoracic)
- GI bleeding
Background

- 156,000 deaths from injury in USA each year
- 93,000 of these involve physical trauma
- \( \frac{1}{2} \) of traumatic deaths occur pre-hospital
- Two most common causes for traumatic deaths =
  - Neurologic injury
  - Uncontrolled bleeding

Most Traumatic Deaths Occur Prior to Or Within 6 Hours of Admission

Background

• ~25% of trauma patients at busy U.S. trauma centers require ≥ 1 RBC unit
• Only 25% of these are massively transfused
• Shock and coagulopathy are associated with massive bleeding and increased mortality

“Triad of Death” in Massive Bleeding Due to Injury

Major trauma insult → Bleeding → Loss of blood → Shock

- Hypoxia
- Hypotension
- Hypovolaemia

Acidosis → Hypothermia

Immunology inflammation Cellular responses Molecular pathways

Lymphocytes Thrombocytes

Pre-existing disease

Drugs and medications

Consumption of clot factors

Fibrinolysis

Endogenous Acute traumatic coagulopathy

Systemic Trauma-Induced coagulopathy

Resuscitation

Dilution
Coagulopathy of Trauma

- Coagulopathy occurs early in trauma patients
- 25-28% of trauma patients present in Emergency Department with coagulopathy
- Severity of coagulopathy correlates directly with mortality

Brohi K et al. Acute traumatic coagulopathy.
Prevention of Death

Keeping severely injured and bleeding patients from dying relies primarily on:

- Early identification of coagulopathy and shock
- Predefined resuscitation strategies to reverse traumatic coagulopathy (and hypovolemia)
- Control of bleeding
- *(and management of acidosis and hyothermia)*

Massive Transfusion Update

Literature Review
Expanded Use of Plasma During Management of Massive Bleeding


Methods

• Retrospective chart review of 246 patients at U.S. Army support hospital, each of whom was massively transfused

• Patients were sorted into 3 groups according to transfused plasma : RBC ratio
  o Low ≈ 1 : 8
  o Medium ≈ 1 : 2.5
  o High ≈ 1 : 1.4

• Mortality rates and causes of death were compared

Results

<table>
<thead>
<tr>
<th>Ratio of Plasma : RBCs</th>
<th>Overall Mortality (p &lt; 0.001)</th>
<th>Hemorrhage Mortality (p &lt; 0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (1:8)</td>
<td>65%</td>
<td>93%</td>
</tr>
<tr>
<td>Medium (1:2.5)</td>
<td>34%</td>
<td>78%</td>
</tr>
<tr>
<td>High (1:1.4)</td>
<td>19%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Logistical regression showed that plasma-to-RBC ratio was independently associated with survival.

Conclusions

• “In patients with combat-related trauma requiring massive transfusion, a high 1:1.4 plasma to RBC ratio is independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage.”

• “For practical purposes, massive transfusion protocols should utilize a 1:1 ratio of plasma to RBCs for all patients who are hypocoagulable with traumatic injuries.”

Analysis of 10 observational studies assessing effects of plasma on mortality in massively bleeding trauma patients.

Plasma : RBC transfusion ratios > 1 : 3 were associated with significantly reduced mortality (OR, 0.38; 95% CI, 0.24-0.60), though the quality of evidence was deemed “very low”

Literature Review

- *Survivor bias* limits utility and interpretability of retrospective studies done to date
- However, no high-quality, sufficiently powered, *randomized controlled trial* had been performed … *UNTIL RECENTLY*
The PROPPR Trial

“Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)”

• Multisite, phase 3 randomized clinical trial comparing efficacy and safety of two different ratios of plasma, platelet, and RBC products (i.e., 1:1:1 versus 1:1:2) received by trauma patients.

• Primary measured outcomes were 24-hour and 30-day mortality rates – used to assess short-term effectiveness and long-term safety profiles, respectively.

• 680 patients were randomized.

These absolute differences were not statistically significant based upon the power of the study. Nevertheless, it was incontrovertible that:

- More patients achieved hemostasis in the 1:1:1 group (86% – versus 78% for the 1:1:2 group; p = 0.006), and …
- Fewer patients in the 1:1:1 group died of exsanguination (9.2% – versus 14.6% for the 1:1:2 group; p = 0.03)

Massive Transfusion Update

Management Recommendations
“It [blood transfusions] saves more lives than you could believe.”

Gen. George S. Patton
Management Recommendations for Massive Bleeding Cases

**Goals include:**

- Early recognition of blood loss
- Maintenance of tissue perfusion & oxygenation by restoration of blood volume and hemoglobin
- Arrest of bleeding including with early surgical and/or radiological intervention
  
  **AND ...**
  
- Judicious use of blood component therapy to correct coagulopathy

From Australian Red Cross Blood Service
Further (Blood-Specific) Discussion of Management Recommendations
Endpoints of Resuscitation When Using RBC Transfusions

- Re-establishment of end-organ perfusion
- Adequate urinary output
- Restoration of vital signs
- Normalization of mixed venous oxygenation
- Clearance of lactic acidosis/base deficit
- Normalization of pH
- Maintenance of Hgb in 7-9 g/dL range
Management Recommendations

Plasma and Other Frozen Components
Management Recommendations

Platelets

BloodSmart
Massive Transfusion Protocols

- New trend (now fixed practice): Give RBCs, Plasma & Platelets to simulate whole blood

- Following ratio is generally used for adults:
  - 6 units RBC Adult (280-350 mL/unit)
  - 6 units Plasma (~ 200-300 mL/unit)
  - 1 Plateletpheresis (equivalent to 6 units of whole blood-derived platelets)
  - (5-10 units Cryoprecipitate)

- A similar ratio (with scaled-down absolute quantities) would be used for children and infants
Massive Transfusion Protocols

• Start sooner (i.e., up front) rather than later by including the yellow stuff,* i.e., ...

• Once a massive transfusion situation has been identified, do not wait until too many RBC units have been administered.

*”Yellow stuff” = Plasma + Platelets
### Management Recommendations

Assess following parameters q30-60 minutes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Targeted Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>35° C</td>
</tr>
<tr>
<td>Acid-base Status</td>
<td>pH &gt; 7.2; base excess &lt; -6; lactate &lt; 4 mM</td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td>&gt; 1.1 mmol/L</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Interpret in context of hemodynamic status and organ and tissue perfusion (and not just w.r.t. “a numeric value”)</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>≥ 50,000/μL</td>
</tr>
<tr>
<td>INR/aPTT</td>
<td>Within ≤1.5 of normal (e.g., INR ≤ 1.6)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>≥ 100-120 mg/dL</td>
</tr>
</tbody>
</table>

From Australian Red Cross Blood Service
Reported Impact of Massive Transfusion Protocols

• “For the 2 years before and subsequent to MTP initiation, there were 4,223 and 4,414 trauma activations, of which 40 and 37 patients, respectively, met study criteria. The FFP : PRBC ratios were identical, at 1 : 1.8 and 1 : 1.8 (p = 0.97).”

• Despite no change in FFP : PRBC ratios, mortality decreased from 45% to 19% (p 0.02).

Reported Impact of Massive Transfusion Protocols

Reported Impact of Massive Transfusion Protocols

“Our data underscore the importance of expeditious product availability and emphasize that massive transfusion is a complex process in which product ratio and time to transfusion represent only the beginning of understanding.”

Pre-Hospital Emergency Transfusions
From 2013 American Heart Association Meeting (J.B. Holcomb et al.)

Background/Methods

• Hypothesis: Pre-hospital transfusion (PHT) of thawed plasma and/or RBCs would result in improved patient coagulation status and survival.
• All patients transfused blood products (either pre- or in-hospital) were included in the study.
• One helicopter system had thawed plasma and RBCs while the other air and ground transport systems used only crystalloid resuscitation.

• Patients receiving PHT were compared with all other patients meeting entry criteria (all comparisons were adjusted in multi-level regression models).
Pre-Hospital Emergency Transfusions
From 2013 American Heart Association Meeting (J.B. Holcomb et al.)

Results

• 6238 adult trauma patients admitted over 15 months
• 577 (9.2% = most severely injured) met inclusion criteria
  ◦ 97 patients received PHT
  ◦ 480 in non-PHT control group.
Pre-Hospital Emergency Transfusions
From 2013 American Heart Association Meeting (J.B. Holcomb et al.)

Results

- 244 units of RBCs and 698 units of plasma were placed on the helicopters, with 1.9% wastage.
- PHT was associated with reduced risks of:
  - 6-hour mortality (adjusted OR=0.08, 95% CI=0.01-0.87, p=0.04)
  - Coagulopathy on arrival (TEG ACT ≥ 128, (adjusted OR=0.40)
  - 13% non-significant improvement in hospital mortality.
Conclusions

• Pre-hospital plasma and RBC transfusion was associated with:
  ○ Improved coagulation status
  ○ Reduced risk of death in the first 6 hours after admission

• Negligible blood product wastage was observed
Management Recommendation: A Case for Thawed (5-Day) Plasma

- During the first 5 days’ storage of thawed plasma, there is very little drop-off in coagulation factor levels.
- Thus, many facilities are using thawed (5-day) plasma almost interchangeably with FFP.
- Benefits
  - Faster turnaround time = Better patient care
  - Reduced product expirations
ABO-Related Product Selection

Group A “Pseudo-Universal” Plasma


• **Methods**: Review of all trauma patients receiving emergency release plasma (Group A) from 2008 to 2011

• **Results**:
  - For 34 of the 254 (14%) patients, these transfusions were incompatible
  - None were observed to have had adverse effects

• **Conclusion**: “Blood banks reticent to adopt massive transfusion protocols owing to supply concerns may safely use Group A plasma”
Other Studies Supporting Urgent Use of Group A “Pseudo-Universal” Plasma

Management Recommendations: Emergent Pre-Transfusion Testing

- Urgently required blood transfusions should not be withheld solely because compatibility testing is incomplete.
- Nevertheless, all parties involved in the transfusion should remember that they face certain increased risks when transfusing blood that has not gone through the “usual” compatibility testing process.
Emergent Release of Blood

• Emergent release involves issuance of RBCs prior to completion of compatibility testing

Massive Transfusion Protocol

• Massive transfusion protocol involves rapid provision of fixed ratios of RBCs, plasma, and platelets (and sometimes cryo); **RBCs may or may not be fully crossmatched**
## Emergently Released versus Fully Crossmatched RBCs: How Long Can You Wait?

<table>
<thead>
<tr>
<th>Time You Can Wait</th>
<th>Type of RBC Available</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 minutes after clot gets to blood bank</td>
<td>O-negative/positive, uncrossmatched</td>
<td>0.2% - 0.6% of population has red cell Ab/s (serious hemolysis rare)</td>
</tr>
<tr>
<td>15 minutes after clot gets to blood bank</td>
<td>Type-specific, uncrossmatched</td>
<td>Risk same as for O-negative/positive</td>
</tr>
<tr>
<td>45 minutes after clot gets to blood bank</td>
<td>Type-specific, crossmatched (unless red cell antibody present)</td>
<td>No RBC antibody found; blood compatible by crossmatch</td>
</tr>
<tr>
<td>90 minutes to several hours</td>
<td>Type-specific; crossmatched in patient with red cell antibody</td>
<td>If blood needed before testing complete, do not withhold</td>
</tr>
</tbody>
</table>
Using Rh-Positive Blood for Rh-Negative Patients

• Only ~ 15% of donor population is Rh-negative.
• If supplies of Rh-negative RBCs are limited, or if very large numbers of RBCs are needed, Rh-positive RBCs often should be used for male and postmenopausal female patients.
• Decision when to switch from Rh-negative to Rh-positive RBCs should be made on a case-by-case basis.
• Rh is far less important for platelets, and not at all important for FFP or cryoprecipitate.
Management Recommendations: Adjunct Care

Methods

- 274 hospitals in 40 countries
- 20,211 adult trauma patients randomized to:
  - Tranexamic acid within 8 hours of injury
  - vs. Placebo
- Primary outcome: Death within 4 weeks

Results

• All cause mortality
  - Tranexamic acid group = 14.5%
  - Placebo group = 16.0% (p = 0.0035)

• Risk of death due to bleeding
  - Tranexamic acid group = 4.9%
  - Placebo group = 5.7% (p = 0.0077)

Conclusions

• “Tranexamic acid safely reduced the risk of death in bleeding trauma patients.”
• “Tranexamic acid should be considered for use in bleeding trauma patients.”

Typical Dose of Tranexamic Acid

- “[L]oading dose of 1 g infused over 10 min, followed by …
- [I]ntravenous infusion of 1 g over 8 h.”
- Initiated “as early as possible to the trauma patient who is bleeding or at risk of significant haemorrhage.”

Spahn DR, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Critical Care 2013, 17:R76
Other Adjuncts to Transfusion Resuscitation

**Calcium Therapy**

“We recommend that ionised calcium levels be monitored and maintained within the normal range during massive transfusion.”

Spahn DR, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Critical Care 2013, 17:R76
Other Adjuncts to Transfusion Resuscitation

Recombinant Factor VIIa

• “We suggest that the use of recombinant activated coagulation factor VII (rFVIIa) be considered if major bleeding and traumatic coagulopathy persist despite standard attempts to control bleeding and best-practice use of conventional haemostatic measures.

• We do not suggest the use of rFVIIa in patients with intracerebral haemorrhage caused by isolated head trauma.”

Spahn DR, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Critical Care 2013, 17:R76
Other Adjuncts to Transfusion Resuscitation

**Fibrinogen**

- Cryoprecipitate – used to treat hypofibrinogenemia
- Plasma, platelets, and RBCs also contain fibrinogen
- High fibrinogen-to-RBC ratio is associated with greater survival (Stinger et al. J Trauma. 2008.)
- Most protocols recommend replacement for plasma fibrinogen levels $\leq 100-120$ mg/dL
Management Recommendations: 

Laboratory Monitoring

• Order following tests q30-60 minutes:
  o Hematocrit/hemoglobin levels
  o Platelet counts
  o PT/INR/aPTT
  o Fibrinogen levels

• Adjust transfusion dosing accordingly

Laboratory Monitoring: Thromboelastography

From Kashuk et al, Annals of Surgery. 2010

Potential Adverse Effects of Massive Transfusion

- Metabolic Disturbances
- Transfusion Reactions
- Infectious Disease Risks
- Other ???
Massive Transfusion Update

Take-Home Messages
Take Home Messages

• Massive transfusion = transfusion replacement of \( \geq 1 \) TBV in \( \leq 24 \) hours (equivalent to \( \sim 8 - 10 \) RBC units in adult) (Note: other definitions also exist)

• Uncontrolled bleeding is one of two most common causes of injury-induced death

• “Triad of death” in trauma =
  - Hypothermia +
  - Acidosis +
  - Coagulopathy

• Traumatic coagulopathy is associated with increased mortality
Many analyses strongly suggest survival advantage with increased plasma and platelet transfusion in massively transfused patients -- Problems with this interpretation include:

- “Survivor bias” and
- Lack of randomized controlled trials … until recently …

The PROPPR trial has largely addressed this issue in support of the following approach …

When transfusing massively bleeding patients …

**Use ~ 1 : 1 : 1 ratio of RBCs-to-plasma-to-platelets**
Tying it up in a neat ...
American College of Surgeons (ACS) Management Recommendations (Applying Directly to Trauma)

**Development of Massive Transfusion Protocols (MTPs)**

“[MTPs] should be developed by a multidisciplinary committee that include, at a minimum, representatives from:

- Transfusion service/blood bank
- Emergency department
- Anesthesia
- Trauma service”

From ACS TQIP (Trauma Quality Improvement Program) Massive Transfusion in Trauma Guidelines, 2013.
ACS Management Recommendations

Development of Massive Transfusion Protocols (MTPs)

“The [MTP] should address:

• Triggers for initiating massive transfusion in trauma
• Resuscitation in the trauma bay, including:
  o MTP product availability
  o MTP product delivery
  o MTP blood product transfusions
• Continuing MTP in the OR, angiography suite, and [ICU]
• Transfusion service processes for delivering blood products
• Transfusion targets
• The use of adjuncts for massive transfusion patients
• Termination of the MTP
• Performance improvement monitoring”

From ACS TQIP Massive Transfusion in Trauma Guidelines, 2013.
ACS Management Recommendations

Triggers for Initiating a Massive Transfusion

“Criteria to activate the MTP should include one or more of the following:

- ABC score of two or more
- Persistent hemodynamic instability
- Active bleeding requiring operation or angioembolization
- Blood transfusion in the trauma bay”

From ACS TQIP Massive Transfusion in Trauma Guidelines, 2013.
ACS Management Recommendations

**Blood Product Resuscitation**

“If MTP criteria are met:

- Begin universal* blood product transfusion rather than crystalloid or colloid solutions
- Transfuse universal* RBC and plasma in a ratio between 1:1 and 1:2 (plasma to RBC)
- Transfuse one unit single donor apheresis or random donor platelet pool for every 6 units of RBC
- Blood products should be automatically sent by transfusion service in standardized ratios

*Note: Most experts agree that it is acceptable to switch to patient-specific (w.r.t. ABO) components as soon as it is safe to do so

From ACS TQIP Massive Transfusion in Trauma Guidelines, 2013.
What About Disciplines Other Than Trauma?

- Trauma
- Obstetrics
- Surgery (e.g., cardiothoracic)
- GI bleeding
Ob Hemorrhage Toolkit Version 2.0

CMQCC
California Maternal Quality Care Collaborative

https://www.cmqcc.org/resources-toolkits/toolkits/ob-hemorrhage-toolkit

Massive Transfusion Update

Summary

- Definitions & Background
- Literature Review
- Management Recommendations
- Take-Home Messages
- Knowledge Assessment
- Q & A
Massive Transfusion Update

Knowledge Assessment
Knowledge Assessment: True or False?

1. A massive transfusion is often defined as when a patient requires approximately one blood volume’s worth of RBCs (e.g., approximately 10 RBC units for a typical adult) within a 24-hour time span.

2. All bleeding patients who require blood transfusions should be initiated on a transfusion product mix of approximately 1 : 1 : 1 RBCs to plasma to platelets.
3. Massively bleeding patients who are constitutively receiving blood products in a fixed ratio never require additional transfusion support for perturbations in their coagulation or platelet profiles.

4. In the setting of massive transfusions, it sometimes may be acceptable to use group A plasma as a “universal” product in lieu of group AB plasma.
Knowledge Assessment: True or False?

5. When managing the needs of any severely bleeding patient, one should wait until the patient’s clinical laboratory results have passed above/below the “trigger point” – e.g.,
   - INR ≥ 1.6 for plasma transfusions;
   - platelet count ≤ 50,000/uL for platelet transfusions;
   - fibrinogen concentration < 100 mg/dL for cryo transfusions

before ordering and transfusing the appropriate blood component(s).
With gratitude to, and respect for, all of my friends and colleagues at PAMET
Thank You ...

Q & A + Other Discussion

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