Massive Transfusion & Hypothermia

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Conflict of Interest

- No relevant conflict of interest to this presentation
- Past participant in *The Great American Fluid Debate* sponsored by Fresenius-Kabi
Objectives

- Define Terms
- Define Risk Factors
- MT Protocols
- “Magic Bullets”
- Complications
- Effects of Hypothermia
- Clinical Management
Major References


- NB Trauma Program Policy Number 2.4-030 Massive Transfusion in the Major Trauma Patient

Definition of Terms

- Historical MT: 10 units PRBC in 24 hours
- Refined to: loss of >50% blood volume in 3 hours
- Best clinical definition: bleeding > 150ml/min
- Historical definition largely useless as early diagnosis is highest priority
Risk Factors

- NIH review: 1.7% of all trauma requires massive transfusion
- 40% decrease since early use of plasma/platelets
- From the outset, highest risk in patients with:
  - INR >1.5
  - pH < 7.25
  - Temp <34C
  - Lactate > 2
Risk Factors

- Likelihood of coagulopathy in patients in shock:
  - 45% - INR > 1.5
  - 25% - Platelets < 150,000
  - 30% - Fibrinogen < 1.0
Risk Factors

- “ABC Score”:
  - FAST (Focused Assessment Sonography for Trauma)
  - BP ≤ 90 systolic
  - Pulse ≥ 110 bpm
  - Penetrating Mechanism

- Presence of 2 or more factors: 75% sensitive & 86% specific to predict need of MT
Pathophysiology

- At rest, O2 delivery equals 4X O2 consumption (i.e. large reserve). If cardiac output maintained, O2 delivery is adequate at HGB 5.0

  **BUT**

- When cardiac output ↑ to maintain BP, oxygen consumption increases, thus higher HGB is required for tissue perfusion

- Exact HGB level unpredictable
Pathophysiology

- Healthy medical students were bled down to HGB 5.3 - intellectual performance ↓ but returned rapidly when re-transfused to HGB > 8.0
- Unhealthy patients may not be able to ↑ cardiac output to maintain tissue oxygenation
- Lactate levels may be useful
Pathophysiology

- Storage lesions in red cells i.e. 2,3 DPG may take 6-24 hrs to normalize but not shown to be clinically important in blood <10 days old
Protocols for Massive Transfusion

- Military and civilian studies show the use of MTP:
  - Increase survival
  - Decreases ICU/hospital length of stay
  - Decreases overall blood product usage

- Right product
- Right time
- Right amount (ratio)
Coagulopathy

- Acute coagulopathy of trauma due to:
  - Massive tissue damage
  - Hypoxia
  - Acidosis
  - Hypothermia
  - Dilution

- Thrombomodulin generated in shock inhibits fibrinogen formation and disinhibits fibrinolysis
Effects of Acidosis

- Factor Xa/Va reduced:
  - 50% at pH 7.2
  - 70% at pH 7.0
  - 80% at pH 6.8
Effects of Hypothermia

- All enzyme activity decreased 7% per degree centigrade
- Prevents platelet activation via traction of glycoprotein Ib/IXa with VWF
- Pathway 50% ablated below 30 degrees centigrade
- Pathway ablation threshold below 34 degrees centigrade
- Massive bleeding with temperature <30 degrees is lethal
Effects of Dilution

- 10% decrease clotting factors and platelets for each 500mls transfused fluid
- Clinical effects seen after 8 units PRBCs in adults
- 10 units PRBC cuts platelet count by 50%
- Critical platelet level = 75,000 (i.e. 50%)
- 1 ‘dose’ of platelets should increase count by 30,000
Effects of Dilution

- Each unit FFP should increase factors by 10% BUT
- Actually only increase by 2.5 %
- ‘Giving nothing but blood products barely keeps up with normal levels of factor and platelets’
Effects of Dilution

- Massive Trauma causes decreased factors and platelets by blood loss, hemodilution and decreased production
- With a ratio of 1:1:1 (packed cells to plasma to platelets):
  - Eventual hematocrit 29%
  - Coagulation factor activity 65%
  - Platelet 8.8 thousand per unit given
# Product Ratios

<table>
<thead>
<tr>
<th>Ratio of Plasma to Red Cells</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (1.0 – 1.4)</td>
<td>81%</td>
</tr>
<tr>
<td>Intermediate (1.0-2.5)</td>
<td>66%</td>
</tr>
<tr>
<td>Low (1-8)</td>
<td>35%</td>
</tr>
</tbody>
</table>
Magic Bullets

- Fibrinogen content:
  - 1 unit fresh whole blood = 1000mg
  - 10 units cryoprecipitate = 2500mg
  - 1 dose platelets = 480mg
  - 1 unit FFP = 400mg
  - 1 unit PRBC = <100mg
Magic Bullets

- Cryoprecipitate:
  - Fibrinogen < 100
  - Volume replete
  - Hypothermic
Magic Bullets

- Factor VIIa:
  - Largely unproven
  - Exceedingly expensive
  - Should not be needed
Magic Bullets

- **FEIBA:**
  - Unproven/studied in trauma patients
  - Expensive
  - Helpful in known fibrinolysis
Magic Bullets

- Tranexamic Acid (TXA):
  - 50 year old drug
  - Good safety profile
  - Proven effective in trauma (CRASH II)
  - Should be given within 3 hours
  - 10% reduction in mortality
  - 15% reduction in bleeding
Complications of Massive Transfusion

- Citrate Toxicity:
  - Metabolized to bicarbonate
  - Metabolic Alkalosis
  - Binds Calcium → hypocalcemia
Complications of Massive Transfusion

- Hypothermia:
  - Conduction
  - Convection
  - Evaporation
  - Radiation
  - 5 units PRBC decreases temperature by 1 degree centigrade
Complications of Massive Transfusion

- Hyperkalemia:
  - Potassium ↑ by 1 mEQ per day/storage
  - Eventual concentration up to 70 mEQ per litre
  - Decreased to 17 mEQ/L by warming/diluting
  - Ideally, use blood less than 10 days old
  - Irradiated blood is more hypokalemic
Complications of Massive Transfusion

- **TRALI:**
  - Occurs within 2 hours of transfusion
  - Resolves within 72 hours
  - Any blood product can cause TRALI
  - ? Due to WBC antibodies
  - Steroids and diuretics are *ineffective*
Volume Status Assessment in Trauma
Predictors of Massive Bleeding

Nunez J Trauma 2009;66:2:346

- 4 factors
  - Penetrating mechanism
  - Trauma sonography
  - Blood pressure <90
  - Pulse >120
- Score >2 is 75% sensitive and 86% specific
Volume Status Assessment in Trauma
Predictors of Massive Bleeding

*McLaughlin J Trauma 2008;64 (s)57*

- Retrospective analysis 3442 patients
- Four factors:
  - Pulse >105
  - BP <110
  - pH <7.25
  - HCT <32
- 66% of these patients will require massive transfusion
Assessment of Volume Status in Trauma

- Vital signs poor predictors of extent of bleeding
- SV02 is better
- Base deficit correlates with:
  - Transfusion requirements
  - ICU Length of Stay
  - Mortality
- Ability to normalize lactate within 24 hours predicts survival
Traditional Approach to Trauma Resuscitation

(As taught to me 1984-1988 Anesthesia Residency)

1. Wrong
2. Wrong
3. Wrong
4. Wrong
5. Wrong
6. Wrong

Rong, Dammit!
1. Trauma patients bleed to death more quickly than you can transfuse them
2. Trauma causing **shock** causes a **coagulopathy**
3. Non-blood fluid resuscitation worsens the coagulopathy by:
   - Diluting factors & platelets
   - Washing off tenuous plugs
   - Worsening hypothermia
   - Worsening acidosis
Acute Coagulopathy of Trauma: A New Disease Entity

Coagulopathy is present on admission in 25% of patients

500% increase in mortality

Only patients in shock are coagulopathic on admission
Acute Coagulopathy of Trauma: A New Disease Entity

- Mechanisms
  - Primary
  - Shock causes increase in thromobomodulin
  - Thromobomodulin has 2 effects:
    - Binds thrombin, preventing it from cleaving fibrinogen
    - TM-T Complex activates thrombin-activatable fibrinolysis inhibitor (TAFI) via activated protein C
  - Activated protein C is a de-inhibitor of fibrinolysis
Effects of Acidosis

- Coagulation proteases optimum pH 8
- Xa/Va complex activity reduced
  - 50% at pH 7.20
  - 70% at pH 7.0
  - 90% at pH 6.8
- Base deficit predicts shock; shock predicts death
- Calcium binding to factors ↓ with acidosis
- Base deficit < 6 = 2% of patients with ↑ PTT and INR
- Base deficit >6 = 20% of patients with ↑ PTT/INR
Effects of Hypothermia

- 9% incidence in trauma
- Serine proteases activity ↓ 5% per 1 degree C
- Platelet activation ↓ 10% per degree C
- Platelet TXA2 release ↓ 15% per degree C
- Clinical bleeding obvious < 34 degrees C
Effects of Hypothermia

Mortality 7% if temperature > 34
Mortality 40% if temperature < 34
Mortality 70% if temperature < 33
Mortality 99% if temperature < 32
Effects of Dilution of Clotting Factors

- Coagulopathy present in:
  - 50% of patients resuscitated with > 3L of non-blood fluid
  - 10% of patients resuscitated with 500ml of non-blood fluid
- Unusual to give warmed fluids in the past
- Amount of fibrinogen in fluid is critical
## Fibrinogen in Fluids

<table>
<thead>
<tr>
<th>Fluid Type</th>
<th>Fibrinogen Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 unit fresh whole blood</td>
<td>1000 mg</td>
</tr>
<tr>
<td>1 bag (10u) cryoprecipitate</td>
<td>2500 mg</td>
</tr>
<tr>
<td>1 dose (6u) platelets</td>
<td>480 mg</td>
</tr>
<tr>
<td>1 unit FFP (250ml)</td>
<td>400 mg</td>
</tr>
<tr>
<td>1 unit PRBCs</td>
<td>&lt; 100 mg</td>
</tr>
<tr>
<td>Colloid/crystalloid</td>
<td>Nada</td>
</tr>
</tbody>
</table>
New Approaches to Shock Resuscitation
Damage Control Resuscitation

McCunn, University of Pennsylvania, 2009

- “Hemostatic” resuscitation
- 1:1:1 red cells, plasma, platelets

Consider using plasma as primary resuscitative fluid

- Borgman J Trauma 2007;63:801
- Spinella Crit Care Med 2007;35:2576
- Stinger J Trauma 2008;64:(s)79
Hemostatic Resuscitation

- Studies show from both military and civilian populations that patients who are resuscitated with high ratios of fibrinogen to red blood cells do much better.

- Mortality in low fibrinogen ratio group: 52-60%
- Mortality in high fibrinogen ratio group: 24-30%

- Optimum BP to perfuse the patient but not wash off plugs:
  - MAP 65
  - Systolic 90
Survival Associations

- Increased survival associated with:
  - Temperature > 34 degrees
  - Blood pressure > 65 mean
  - Hematocrit > 30
  - Base deficit < 6
Survival Associations

- The only independent predictor of mortality is low fibrinogen ratio
- High fibrinogen ratio \( \uparrow \) survival and:
  - \( \downarrow \) Blood loss
  - \( \downarrow \) Blood product usage
  - \( \downarrow \) ICU LOS
Resuscitation Strategies

- Vandromme: J Trauma 2011: 70:384-90
- Massive transfusion risk identified by PREHOSPITAL SHOCK INDEX (SI):
  - SI = HR/SBP
  - Normal SI = < 0.7
- 8011 patients studied, 276 massively transfused
### Resuscitation Strategies

<table>
<thead>
<tr>
<th>Shock Index (SI)</th>
<th>Risk of Mortality (field)</th>
<th>Risk of Mortality (ER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0.9</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt; 1.1</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>&gt;1.3</td>
<td>8</td>
<td>20</td>
</tr>
</tbody>
</table>
Resuscitation Strategies
Other methods to predict massive transfusion risk:

- **ABC** (assessment of blood consumption)
  - FAST ultrasound
  - BP < 90
  - P > 120
  - Penetrating Mechanism

- **TRASH** (trauma associated severe hemorrhage)
  - ABC plus HGB < 100 and base excess

- **McLaughlin Score**:
  - BP < 110
  - Pulse > 105
  - pH < 7.25
  - HCT < 32
Resuscitation Strategies

Nirula (J Trauma, 2010; 69:595-601)

- “Scoop & Run to the Trauma Centre or Stay & Play at the Local Hospital: Hospital transfer Effects on Mortality”
- 1112 patients – 318 initially triaged to non-trauma centre
# Resuscitation Strategies

*Nirula* *(J Trauma, 2010; 69:595-601)*

<table>
<thead>
<tr>
<th></th>
<th>Non-Trauma Centre</th>
<th>Trauma Centre</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crystalloid</strong></td>
<td>4200</td>
<td>400</td>
</tr>
<tr>
<td><strong>Risk of Blood Transfusion</strong></td>
<td>12 (60%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td><strong>Mortality Risk</strong></td>
<td>3.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Permissive hypotension
Limited fluid resuscitation

Many large animal model studies have been performed to discover “when does the clot pop off”?

= 80 mmHg systolic BP

“Well-informed resuscitationists will DISALLOW blood pressure cuffs as a measure of success of fluid therapy
Kenneth Mattox, Baylor College
Houston, Texas (2005)

DO
THEY
HAVE
A
RADIAL
PULSE?
Kenneth Mattox, Baylor College Houston, Texas (2005)

- Thromboelastography studies show that trauma patients who are hypotensive (therefore coagulopathic) recover much faster if they are given little or no fluid than if they are aggressively resuscitated with crystalloid

- “25 ml colloid boluses Q5 Min until return of radial pulse” THEN NO MORE FLUID UNTIL BLEEDING CONTROLLED
Current Management Principles

Massive Transfusion Protocols

1. Very early use of plasma/colloid
2. Minimal use of crystalloid
3. Goal is euvolaemia
4. Avoid red cell storage lesions by using fresh product (< 14 days old)
Current Management Principles

Massive Transfusion Protocols

5. Cell salvage wherever possible

6. “Transfusion packs” approximating whole blood as damage control

7. Evaluation of coagulation by thromboelastography
Advantages of MTPs

- Dramatic, life-saving results
- Mortality ↓ by 50%
- Avoidance of expensive and unproven magic bullets (O’Keefe, 2008)
  - Factor VIIa, Octoplex, FEIBA
- Overall decreased blood product usage
  - (O’Keefe Arch Surg 2008;143:686)
- Decreases ICU ventilator days, blood use & LOS
  - (Gonzalez, J Trauma, 2008;64:247)
APPENDIX B: MASSIVE TRANSFUSION ALGORITHM

Massive Blood Loss Identified
MT Protocol Initiated
Initial Blood Work Drawn

SBP ≤ 90 or 100 with Head Injury & GCS<13?
No
Await type specific blood products

Yes

- Avoid excessive crystalloid or artificial colloid use. Transfuse plasma as early as possible for volume expansion and correction of coagulopathy

- RhNegative preferred for children and women of child bearing years. Otherwise consider Rhig pm at termination of transfusion

Bolus 1-2 litres of warmed Ringer’s lactate *(10-20 mL/Kg)

SBP still ≤ 90 or 100 with Head Injury & GCS<13?
No
Await type specific or crossmatched blood products

Yes

Lab will provide universal*** donor blood and products until type specific is available

Ensure IV fluid is changed to NaCl prior to administering blood/blood products

For adult patients with significant ongoing hemorrhage, consider tranexamic acid 1g IV bolus over 10 minutes, then 1g IV infusion over 8 hours. Available from Pharmacy. Aim to initiate within 3 hours of injury.

Level I, II and III Trauma Centres
RBC: 4 units
Plasma: 500 mL
Platelets: 1 dose when available

Level V Trauma Centres
RBC: 2 units
Plasma: 500 mL

Consult Transfusion Medicine Laboratory for pediatric dosing

Level I, II and III Trauma Centres
RBC: 4 units
Plasma: 500 mL or as required
Platelets: 1 dose when available

Level V Trauma Centres
RBC: 2 units
Plasma: 500 mL

Initiate and continue transfusion and revert to goal directed treatment once lab data becomes available.

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The Priority of Plasma

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q30 min, unless requested sooner

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An oasis of knowledge in the desert of ignorance…