Critical Bleeding and Trauma

Peter T. Clark
FACEM, FJFICM, FANZCA

Intensive Care Units Westmead Hospital & Westmead Private Hospital
Careflight Medical Retrieval Service
Deputy Director NSW Medical Retrieval Unit
Director NSW Institute Trauma & Injury Management
Many trauma patients require blood transfusion

- ~10-20% of all trauma patients receive one or more transfusions\(^1\)
- ~50% of trauma patients admitted to an ICU will receive transfusions\(^2\)
- 1-2% of trauma patients require "massive transfusion" (>20 units of red blood cells)\(^3\)

\(^1\) Annual Report German Trauma Register 2002
\(^2\) MOF is multiple organ failure: Shapiro, J. Trauma 2003; 55:269-274
\(^3\) Wudel, J. Trauma 1991; 31: 1-7
Management of bleeding following major trauma: a European guideline
Donat R Spahn¹, Vladimir Cerny², Timothy J Coats³, Jacques Duranteau⁴, Enrique Fernández-Mondéjar⁵, Giovanni Gordini⁶, Philip F Stahel⁷, Beverley J Hunt⁸, Radko Komadina⁹, Edmund Neugebauer¹⁰, Yves Ozier¹¹, Louis Riddez¹², Arthur Schultz¹³, Jean-Louis Vincent¹⁴ and Rolf Rossaint¹⁵

This article is online at: http://ccforum.com/content/11/1/R17
Control Bleeding - 12 P’s

Prior to Development Coagulopathy

Apply **Pressure** With **Packs** or **Pads**, Have **Patience**, Suture With **Prolene** (or Whatever).

Give **Platelets**, Fresh Frozen **Plasma**, **Protamine** (to Reverse Heparin), and **Packed** Cells (If Still Bleeding), Call the **Professor** for Help……If He Can’t Help **Pray**….That You Will Not Meet Your Patient at **Postmortem**

(Dr A Assalia)
Coagulopathy

Bleeding From Unnamed Vessels Due to Incompetent Clotting Mechanism That Is Not Controllable by the Efforts of a Competent Surgeon...

- Bleeding Tendency
- Multi-factorial
- Preventable (?!)
- Surgeons Detect Early - Laboratory Results Abnormal Late
Coagulopathy

The Coagulopathy of Trauma: A Review of Mechanisms


- Can occur early in trauma.
- Key initiators
  - Tissue trauma
  - Shock
  - Dilution
  - Hypothermia
  - Acidemia
  - Inflammation
Median mortality for trauma patients with coagulopathy on presentation ranges from 19 to 62 % vs 6 to 11% for those without coagulopathy
Physiology of Haemostasis

- COAGULATION
- Anticoagulation
- Fibrinolysis

TF-VIIa → X → Xa → II → Thrombin → I → Fibrin

IX → IXa → Va + VIIIa

XI → Xla

XII → XIIa
Coagulopathy Causes

- Bleeding / Consumption: Factors Depleted by Clot Formation
- ‘Washout’: Resuscitation With Intravenous Fluids Dilutes Normal Clotting Proteins and Platelets, Impairing Function
- Hypothermia: Low Temperature Inhibits Clotting Protein and Platelet Function, Slows Fibrin Formation / Speeds Fibrinolysis
- Metabolic Derangements: Acidosis and Hypocalcaemia Are Common in Shock / Resuscitation; Both Compromise Clotting
Optimal Treatment of Coagulopathy

- Search for Patients at Risk
  - Discover All Major Bleeding Sources Fast
  - Realise the Severity Injury
- Treat It As Soon As It Develops
  - Operate on Relevant Bleeding Sources
  - Treat Coagulopathy
25% of major trauma patients presenting to hospital have a coagulopathy at presentation

- Widespread evidence for coagulopathy as an independent predictor of outcome
- This is associated with both increased anatomical injury (ISS >16) & shock (BXS > -6)
- The mechanism is complex and involves activation of protein C leading to fibrinolysis and Thrombomodulin formation at the expense of Fibrin
- The classical factors (acidosis, hypothermia, consumption and dilution) may contribute but do not appear to be the initiating factor
FFP, Clotting factors and Platelets

- Most patients with severe bleeding develop a dilutional coagulopathy

- Blood components should be given before the coagulopathy becomes severe enough to make it worse

Possibly more important than blood
FFP, clotting factors and platelets

- By the time 10 units replaced, patient has lost 70% original plasma and has slight prolongation of PT, APTT
- By the time 12-20 units transfused platelets<100 (because sequestered in spleen =60% N)
- 6 Units FFP will correct coagulation, but patient will have factor levels approx 60% of normal
Haemostatic defects

Coagulation factors

- Require 30% of N for coagulation-usually less than this after 10 units packed cells
- 1 unit FFP contains 80% of plasma from 1 unit whole blood, 500mg fibrinogen and 200 IU all clotting factors
- 5 FFP replace 25% factors, 1L volume
Haemostatic defects

Platelets
- Dilution of platelets after 12-20 units to <100, treat when <50. 1 unit raises by 5 -10

Cryoprecipitate
- Contains high concentration of VWF, F VIII, fibrinogen.
  Fibrinogen rapidly reduced by haemodilution, critical for clot formation and F VIIa action 1 unit per 10kg raises fibrinogen by 50mg/l
The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital
Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

- Retrospective review of 246 patients in a US field hospital in Iraq (2003-5) who received > 10 units PRC in 24 hrs. 94% had penetrating injury
- Defined as: Low ratio (1:8) (n=31) Medium ratio (1:2.5) (n=53) High Ratio (1:1.4) (n=162) in relation to PRC: Plasma
- Crude mortality Low ratio 65%, Medium ratio 34%, High ratio 19%
- Multivariate logistic regression analysis identified high PRC: Plasma as the most important factor in survival prediction OR 8.6 (2.1-35)
An FFP:PRBC Transfusion Ratio ≥1:1.5 Is Associated With A Lower Risk Of Mortality After Massive Transfusion

Jason L. Sperry, MD, MPH, Juan B. Ochoa, MD, Scott R. Gunn, MD, Louis H. Alarcon, MD, Joseph P. Minei, MD, Joseph Cuschieri, MD, Matthew R. Rosengart, MD, MPH, Ronald V. Maier, MD, Timothy R. Billiar, MD, Andrew B. Peitzman, MD, Ernst E. Moore, MD, and The Inflammation the Host Response to Injury Investigators

- Retrospective, multi center, civilian, US study of x pts who required > 8 units of blood in the first 12 hours. All had blunt trauma with hypotension and shock
- Defined as PRC : Plasma High ratio (>1.5:1) (n=102) or Low Ratio (<1.5:1) (313)
- Crude mortality High ratio 28%, Low ratio 35% (p 0.21)
- Multivariate logistic regression identified High PRC : Plasma as the most important predictor of mortality OR 1.93 (1.23-3.02)
Retrospective study of 466 patients at 16 civilian centers in the US who received > 10 units PRC in 24 hrs (2005-6). About 2/3rds blunt trauma

Defined as PRC: Plasma Low ratio (<1.4:1) (n=102), Medium ratio (1.4-1:1) (n=299) or High ratio (< 1:1). Also defined the same ratios for PRC: Platelets

Crude hospital mortality PRC: Plasma: High ratio 25%, Medium ratio 41%, Low ratio 54%. PRC: Platelets: High ratio 27%, Medium ratio 46% Low ratio 43%
Component therapy

- Policy
- Communication
  - Regular updates patient status, forecasting Tx requirements, timely FBC, Coags
- Clear role definition
Other Component therapy

- Biostate-human F VIII, 250 IU/vial
- Prothrombinex-HT – F IX, F11, F X, F V, F VII
- Risk of thrombosis as many of the factors are activated
- Use in conjunction with Haematologist advice
Normal Coagulation and the role of Factor VII a

- Primary Haemostasis-platelet plug, platelets adhere to endothelium
- Secondary haemostasis-platelets stimulate sequential activation of coagulation factors, formation of fibrin mesh
NovoSeven® (rFVIIa) controls bleeding at the site of vascular injury

- rFVIIa works locally at the site of vascular injury, where tissue factor (TF) is exposed and activated platelets are found.
- Binding of factor VIIa or rFVIIa to TF initiates the coagulation generating small amounts of thrombin.
- At pharmacological doses rFVIIa directly activates factor X on the surface of activated platelets resulting in a "thrombin burst".
- The thrombin burst leads to the formation of a stable haemostatic plug which controls the bleeding.

Adapted from Hoffman M et al., 2001.
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>CI</th>
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<tbody>
<tr>
<td>rVIIa</td>
<td>2.5</td>
<td>0.8-7.6</td>
</tr>
<tr>
<td>pH</td>
<td>24.8</td>
<td>2.3 – 268</td>
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<tr>
<td>Platelet count</td>
<td>1.004</td>
<td>1.00 – 1.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.96 – 0.99</td>
</tr>
<tr>
<td>Head Injury</td>
<td>0.7</td>
<td>0.6 – 0.8</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.3</td>
<td>0.2 – 0.5</td>
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</tbody>
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J Trauma 2006;61
Recombinant VIIa (Novo Seven)

Novo Seven (Recombinant VIIa)

- Dose of 60 µg/kg to 100 µg/kg may be up to 200 µg/kg
  - Monitor response over the next 15-20 minutes.
  - Further dosing may be required if the response is inadequate.
Fibrinolytic Therapy

- Aprotonin (Trasylol)
  - Serine protease inhibitor
  - Anti-inflammatory properties
  - Cochrane reviews, Mangano, BART study

- Tranexamic acid
  - CRASH-2
    - 1 g of tranexamic acid infused over 10 min, followed by an intravenous infusion of 1 g over 8 h

- ε Aminocaproic Acid (Amicar)
  - Derivative and analogue of lysine,
    - Effective inhibitor for proteolytic enzymes like plasmin
Haemostatic defects

- 5 units of packed cells
  - Lower temperature by 1° C
- 7 units of packed cells
  - Lower the base excess by 1
Haemostatic defects

Hypothermia

- Begins at time of injury
- Resuscitation fluids
- Coagulation enzyme activity reduced by 10% per 1°C
- Hypothermia impairs platelet function
- Effect usually clinical < 34°C ++ < 30°C
Haemostatic defects.

Acidosis

- Reduces coagulation enzyme activity
- Impairs platelet function
- All become abnormal at pH<6.8
- 50% of normal when pH<6.4
Management Massive Transfusion

- After Transfusion 4 Units Packed Cells:
  - Take Coagulation tests & FBC - label URGENT and send to laboratory
  - Liaise with the Consultant on call to discuss / advise on replacement therapy as necessary.
- Fresh Frozen Plasma should be started and cryoprecipitate is likely to be required
Management Massive Transfusion

- After Transfusion of 10 Units of packed red cells:
  - Patient should have received at least 8 units FFP & at least 8 units Cryoprecipitate & Platelets
  - Coagulation tests (including Fibrinogen & FDP’s) & FBC should be repeated
  - Consider CaCl$_2$
Management Massive Transfusion

- After Transfusion of 10 units of packed red blood cells, the following should be asked:
  - Does the patient still have a coagulopathy?
    - If YES - prescribe with advice / assistance combinations of Factor VIII, Factor IX, FFP, Cryoprecipitate and Platelets as replacement therapy; as well as consideration of Factor VIIa
    - If NO - that is the patient has near normal coagulation profile, but is still bleeding, then a "second" look procedure or radiological intervention will generally be required.