Critical Bleeding and Major Haemorrhage Protocols

Dr Anastazia Keegan
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The management of life-threatening bleeding is challenging.
Major Haemorrhage: Physiological Definition

Adults
Loss of \( \geq 1 \) blood volume in 24 hours or
Loss of \( \geq 50\% \) of blood in 3 hour or
Loss of \( \geq 150 \) ml of blood per minute

Children
Loss of \( >40 \) mL/kg of blood volume
Major Haemorrhage: Transfusion Medicine Definition

• > 10 units of red cells in 24 hours
• ≥ 4 units of red cells within 4 hours
Major Haemorrhage: Clinical Settings

• Perioperative Haemorrhage
  • Cardiothoracic Surgery
  • Vascular Surgery
  • Liver transplantation

• Gastrointestinal Haemorrhage
  • Upper GI
  • Lower GI

• Obstetric Haemorrhage
  • Trauma
3566 massive transfusion (MT) patients identified from 20 hospitals in Australia and New Zealand

Figure 1. Participating MTR sites and number of MT patients identified

*N=number of MT patients identified
Perioperative Haemorrhage

- Australian Audit of Surgical Mortality, 2013
  - 11% of surgical mortality was due to uncontrolled bleeding
3566 massive transfusion (MT) patients identified from 20 hospitals in Australia and New Zealand

- Other Surgery: 764 MT cases
- CT Surgery: 707 MT cases
- Trauma: 591 MT cases
- GI Haemorrhage: 494 MT cases
- Vascular Surg: 367 MT cases
- Obstetrics: 211 MT cases
- Liver Transplant: 169 MT cases
- GIHaem + SurgBleed: 121 MT cases
- Medical/Other: 103 MT cases
- CT+VascSurgBleed: 39 MT cases

Total MT cases: 3566

Percentage of MT cases: 57%
Gastrointestinal Haemorrhage

• Mortality of Upper GI bleeds: 6-10%
  • Incidence decreasing
• Mortality of Lower GI bleeds: 4-10%
  • Incidence increasing

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3566 massive transfusion (MT) patients identified from 20 hospitals in Australia and New Zealand.
Trauma

• Trauma is the leading cause of death < 35 years
  • Up to 40% of mortality

• Risk factors associated with increased mortality
  • > 55 years (OR: 4.7)
  • GCS ≤8 (OR: 4.6)
  • ≥20 units PRBC (OR: 3.3)
  • Prothrombin Time (OR: 3.2)
  • ISS ≥ 24 (OR: 2.9)
3566 massive transfusion (MT) patients identified from 20 hospitals in Australia and New Zealand

- Other Surgery: 764 cases
- CT Surgery: 707 cases
- Trauma: 591 cases
- GI Haemorrhage: 494 cases
- Vascular Surg: 367 cases
- Obstetrics: 211 cases
- Liver Transplant: 169 cases
- GIHaem + SurgBleed: 121 cases
- Medical/Other: 103 cases
- CT+VascSurgBleed: 39 cases

17%
Obstetric Haemorrhage

- PPH is one of the leading causes of maternal mortality
- Increasing incidence
- PPH mortality rates in WA: 7.4 per 100,000 live births
3566 massive transfusion (MT) patients identified from 20 hospitals in Australia and New Zealand

- Other Surgery: 764 cases
- CT Surgery: 707 cases
- Trauma: 591 cases
- GI Haemorrhage: 494 cases
- Vascular Surg: 367 cases
- Obstetrics: 211 cases
- Liver Transplant: 169 cases
- GI Haem + Surg Bleed: 121 cases
- Medical/Other: 103 cases
- CT + Vasc Surg Bleed: 39 cases

6%
KEEP CALM AND ACTIVATE THE MAJOR HAEMORRHAGE PROTOCOL
Major Haemorrhage Protocols

• Evidence-guided transfusion guidelines

• Defined algorithms for blood product ordering, preparation and delivery

• Facilitate communication between treating clinicians, laboratory and transfusion medicine

• *Aimed to improve patient outcomes*
Major Haemorrhage Protocol
Fiona Stanley Hospital

Critical Bleeding defined by > 3
- HR > 120bpm
- BP < 90mmHg
- Haemoglobin < 90g/L
- INR > 1.5
- pH < 7.35
- Temperature < 35°C

Critically Bleeding Patient with Haemodynamic Instability

Call “SS” to activate “MAJOR HAEMORRHAGE PROTOCOL”
Inform TMU “28005”
Senior clinician to inform TMU if ROTEM is to be used to guide transfusions

No ROTEM
- MHP Pack 1
  - RBC 4 units
  - FFP 2 units

REMEMBER
- Temperature > 36°C
- pH > 7.35
- Ca++ > 1.12mmol

MHP Pack 2
- RBC 4 units
- FFP 2 units
- Platelets 1 adult dose

MHP Pack 3
- RBC 4 units
- FFP 2 units
- Cryoprecipitate 8 units

Regular reassessment with Full Blood Count & Coagulation profile every 30-60mins
Consider discussing with Haematologist on-call

Bleeding controlled, patient stable or deceased
Stop MHP by notifying TMU “28005”
Return unused products to TMU

ROTEM
- RBC 4 units
- Blood components guided by ROTEM
- Repeat ROTEM 10mins after blood components given

Transfusion Recommendations
- FIBTEM A10 < 10mm or Fibrinogen < 1.5g/L
- Cryoprecipitate 8 units
- EXTEM A10 < 40mm or Platelets <80 x 10^9/L
- Platelets 1 adult dose
- EXTEM CT > 90 sec or APTT > 50 or INR > 1.5
- FFP 4 units
- EXTEM ML > 15%
- 1g Tranexamic Acid

Special Circumstances
- Warfarin
  - 10mg Vitamin K
  - 50IU/kg Prothrombinex
- Aspirin/Clopidogrel
  - Platelets 1 adult dose
- Bleeding disorder, coagulopathy or NOAC
  - Contact haematologist

Trauma
- 1g Tranexamic Acid
  - within 3hrs
- Cryoprecipitate 16units
- Obstetric
- Haemorrhage
  - Cryoprecipitate 16units
Major Haemorrhage Protocols: Controversies

• Testing modalities
  • Standard laboratory tests vs Point of Care testing

• Resuscitation Strategy
  • Fixed ratio transfusion vs Targeted transfusion
Major Haemorrhage Protocols: Controversies

• Transfusion Targets and Triggers
  • Fresh products vs Fractionated Products vs Concentrates

• Special Circumstances
  • Tranexamic Acid, Fibrinogen concentrate
    • Recombinant Factor VIIa
Activation of the Major Haemorrhage Protocol

- Critically bleeding patient with haemodynamic instability
- Senior clinician calls “55”
  - “Activate Major Haemorrhage Protocol”
  - Text page sent to Duty Anaesthetist
  - Text page sent to Transfusion Medicine
- Contact Transfusion Medicine
  - “Activate Major Haemorrhage Protocol”
  - Provide clinical information about the patient and their location
- Senior clinician determine if ROTEM will guide blood product transfusion

Critically Bleeding Patient with Haemodynamic Instability

Call “55” to activate “MAJOR HAEMORRHAGE PROTOCOL”

Inform TMU “28005”

Senior clinician to inform TMU if ROTEM is to be used to guide transfusions
Major Haemorrhage Protocols

• Testing modalities
  • Standard laboratory tests vs Point of Care testing

• Resuscitation Strategy
  • Fixed ratio transfusion vs Targeted transfusion

• Transfusion Targets and Triggers
  • Fresh products vs Fractionated Products vs Concentrates

• Special Considerations
  • Tranexamic Acid, Fibrinogen replacement
    • Recombinant Factor VIIa
Laboratory Monitoring
During Major Haemorrhage

Standard Laboratory Tests
• Group and Screen
• Coagulation Profile (APTT, PT, INR and Fibrinogen)
  • Full blood count (Hb, Platelets)
  • Biochemistry (Ca, Lactate)

VS

Point of Care Tests
ROTEM and TEG
Standard Laboratory Tests

• Advantages
  • Precise and accurate assessment of components of intrinsic and extrinsic coagulation cascade
    • Diagnosis of haemophilia
    • Therapeutic monitoring (Warfarin, Heparin)

• Disadvantages
  • Long turn around times
  • Performed on plasma
  • Can not assess fibrinolysis
Point of Care Testing

• Measures the viscoelastic properties of whole blood under low shear conditions

• Assesses all stages of clot formation, clot stability and clot lysis
Temograms

- CT: Clotting time
- CFT: Clot formation time
- alpha: Alpha-angle
- A10: Amplitude 10 min after CT
- MCF: Maximum clot firmness
- LI30: Lysis index 30 min after CT
- ML: Maximum lysis
Point of Care Testing

• **Advantages**
  • Global assessment of haemostasis including fibrinolysis
    • Whole blood
    • Point of care
    • Rapid turn around times

• **Disadvantages**
  • Limited quality evidence in clinical scenarios
    • Variable clinical uptake
    • No QC program
  • Insensitive to VWD, anti-platelet drugs and NOACs
But, What’s the Evidence?
Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion (Review)

Afshari A, Wikkelso A, Brok J, Moller AM, Wetterslev J
## Results

### Analysis 1.1. Comparison | Mortality: TEG or ROTEM versus control group, Outcome | Longest follow-up mortality: TEG & ROTEM vs control.

Review: Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion

Comparison: | Mortality: TEG or ROTEM versus control group
Outcome: | Longest follow-up mortality: TEG % ROTEM vs control

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TEG%ROTEM n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H.Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H.Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Av. 2009</td>
<td>3/114</td>
<td>2/110</td>
<td>16.4%</td>
<td>1.45 [0.25, 8.50]</td>
<td></td>
</tr>
<tr>
<td>Girauskas 2010</td>
<td>4/27</td>
<td>5/29</td>
<td>38.9%</td>
<td>0.86 [0.26, 2.87]</td>
<td></td>
</tr>
<tr>
<td>Royston 2001</td>
<td>0/30</td>
<td>0/30</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shore-Lesserson 1999</td>
<td>0/53</td>
<td>2/52</td>
<td>20.4%</td>
<td>0.20 [0.01, 3.09]</td>
<td></td>
</tr>
<tr>
<td>Wang 2010</td>
<td>2/14</td>
<td>3/14</td>
<td>24.2%</td>
<td>0.67 [0.13, 3.40]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>238</strong></td>
<td><strong>235</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.77 [0.35, 1.72]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 9 (TEG%ROTEM), 12 (Control)
Heterogeneity: Chi² 1.34, df = 3 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences; Not applicable
Results

Analysis 3.2. Comparison 3 Bleeding: TEG or ROTEM versus control, Outcome 2 12-hour mediastinal tube drainage & postoperative bleeding (mL).

Review: Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion.

Comparison: 3 Bleeding: TEG or ROTEM versus control

Outcome: 2 12-hour mediastinal tube drainage % postoperative bleeding (mL)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TEG % ROTEM Mean(SD)</th>
<th>Control Mean(SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ak 2009</td>
<td>114 480.5 (351)</td>
<td>110 591.4 (339.2)</td>
<td>-110.90 [-201.29, -20.51]</td>
<td>43.9 %</td>
<td></td>
</tr>
<tr>
<td>Girdauskas 2010</td>
<td>27 600 (422.22)</td>
<td>29 680 (407.41)</td>
<td></td>
<td>10.4 %</td>
<td>-80.00 [-297.60, 137.60]</td>
</tr>
<tr>
<td>Nuttal 2001</td>
<td>41 420 (425)</td>
<td>51 670 (687.5)</td>
<td></td>
<td>9.5 %</td>
<td>-250.00 [-479.18, -208.2]</td>
</tr>
<tr>
<td>Royston 2001</td>
<td>30 470 (388.9)</td>
<td>30 390 (429.6)</td>
<td></td>
<td>11.4 %</td>
<td>80.00 [-127.36, 287.36]</td>
</tr>
<tr>
<td>Westbrook 2009</td>
<td>32 875 (277.778)</td>
<td>37 960 (281.481)</td>
<td></td>
<td>24.9 %</td>
<td>-85.00 [-217.25, 47.25]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>244</td>
<td>257</td>
<td>100.0 %</td>
<td>-92.68 [-165.82, -19.55]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1015.75; Chi² = 4.65, df = 4 (P = 0.32); I² =14%
Test for overall effect: Z = 2.48 (P = 0.013)
Test for subgroup differences: Not applicable
Main results

We included nine RCTs with a total of 776 participants; only one trial had a low risk of bias. We found two ongoing trials but were unable to retrieve any data from them. Compared with standard treatment, TEG or ROTEM showed no statistically significant effect on overall mortality (3.78% versus 5.11%, RR 0.77, 95% CI 0.35 to 1.72; I² = 0%) but only five trials provided data on mortality. Our analyses demonstrated a statistically significant effect of TEG or ROTEM on the amount of bleeding (MD -85.05 ml, 95% CI -140.68 to -29.42; I² = 26%) but failed to show any statistically significant effect on other predefined outcomes.

Authors’ conclusions

There is an absence of evidence that TEG or ROTEM improves morbidity or mortality in patients with severe bleeding. Application of a TEG or ROTEM guided transfusion strategy seems to reduce the amount of bleeding but whether this has implications for the clinical condition of patients is still uncertain. More research is needed.
Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems)

1 Recommendations

Cardiac surgery

1.1 The ROTEM system and the TEG system are recommended to help detect, manage and monitor haemostasis during and after cardiac surgery.

1.2 The Sonoclot system is only recommended for use in research to help detect, manage and monitor haemostasis during and after cardiac surgery. Research is recommended into the clinical benefits and cost effectiveness of using the Sonoclot system during and after cardiac surgery (see section 7.1).

1.3 Healthcare professionals using the ROTEM system and the TEG system during cardiac surgery should have appropriate training and experience with these devices.
Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding (Review)

Hunt H, Stanworth S, Curry N, Woolley T, Cooper C, Ukoumunne O, Zhelev Z, Hyde C

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 2

http://www.thecochranelibrary.com
Authors’ conclusions

We found no evidence on the accuracy of TEG and very little evidence on the accuracy of ROTEM. The value of accuracy estimates are considerably undermined by the small number of included studies, and concerns about risk of bias relating to the index test and the reference standard. We recognise that the reference standards of PT and INR are imperfect, but in the absence of embedded clinical consensus these are judged to be the best reflection of current clinical practice. We are unable to offer advice on the use of global measures of haemostatic function for trauma based on the evidence on test accuracy identified in this systematic review. This evidence strongly suggests that at present these tests should only be used for research. We consider more thoroughly what this research could be in the Discussion section.
Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems)

NICE diagnostics guidance [DG13] Published date: August 2014

Emergency control of bleeding

1.4 There is currently insufficient evidence to recommend the routine adoption of viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems) in the NHS to help detect, manage and monitor haemostasis in the emergency control of bleeding after trauma and during postpartum haemorrhage. Research is recommended into the clinical benefits and cost effectiveness of using viscoelastometric point-of-care testing to help in the emergency control of bleeding after trauma or during postpartum haemorrhage (see section 7.2).
Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence?

T. Haas¹, D. Fries², K. A. Tanaka³, L. Asmis⁴, N. S. Curry⁵ and H. Schöchl⁶,⁷

Summary. Standard laboratory coagulation tests (SLTs) such as prothrombin time/international normalized ratio or partial thromboplastin time are frequently used to assess coagulopathy and to guide haemostatic interventions. However, this has been challenged massive bleeding setting. Medline was searched for investigations using results of SLTs as a means to determine coagulopathy or to guide bleeding management, and the outcomes (i.e. blood loss, transfusion requirements, mortality) were reported. A total of 11 guidelines for management of massive bleeding or perioperative bleeding and 64 studies investigating the usefulness of SLTs in this setting were identified and were included for final data synthesis. Referenced evidence for the usefulness of SLTs was found in only three prospective trials, investigating a total of 108 patients (whereby microvascular bleeding was a rare finding). Furthermore, no data from randomized controlled trials support the use of SLTs. In contrast, numerous investigations have challenged the reliability of SLTs to assess coagulopathy or guide bleeding management. There is actually no sound evidence from well-designed studies that confirm the usefulness of SLTs for diagnosis of coagulopathy or to guide haemostatic therapy.

Editor’s key points

• The authors review the evidence for the continued use of standard laboratory tests of coagulation.

• They conclude that there is minimal evidence for the use of standard laboratory tests in guiding the management of perioperative bleeding.
Guidelines

Management of severe perioperative bleeding Guidelines from the European Society of Anaesthesiology

2 SUMMARY: RECOMMENDATIONS, SUGGESTIONS AND STATEMENTS
Grade of recommendation shown in bold type (see Table 1)

Evaluation of coagulation status
We recommend the use of a structured patient interview or questionnaire before surgery or invasive procedures, which considers clinical and family bleeding history and detailed information on the patient’s medication. 1C

We recommend the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, PT and platelet count in elective surgery. 1C

We recommend the application of transfusion algorithms incorporating predefined intervention triggers to guide haemostatic intervention during intraoperative bleeding. 1B

We recommend the application of transfusion algorithms incorporating predefined intervention triggers based on point-of-care (POC) coagulation monitoring assays to guide haemostatic intervention during cardiovascular surgery. 1C

Evaluation of platelet function We suggest preoperative platelet function testing only in addition to a positive bleeding anamnesis. 2C

Table 1. Grades of recommendation – GRADE system
Major Haemorrhage Protocol
Fiona Stanley Hospital

Critical Bleeding defined by > 3
 HR > 120bpm
 BP < 90mmHg
 Hb < 90g/L
 INR > 1.5
 pH < 7.25
 Temperature < 35°C

Critically Bleeding Patient with Haemodynamic Instability

Call “55” to activate “MAJOR HAEMORRHAGE PROTOCOL”
Inform TMU “28005”
Senior clinician to inform TMU if ROTEIM is to be used to guide transfusions

No ROTEIM

MHP Pack 1
RBC 4 units
FFP 2 units

REMEMBER
Temperature > 36°C
pH > 7.35
Ca++ > 1.12mmol

ROTEIM

RBC 4 units
Blood components guided by ROTEIM
Repeat ROTEIM 10mins after blood components given

MHP Pack 2
RBC 4 units
FFP 2 units
Platelets 1 adult dose

MHP Pack 3
RBC 4 units
FFP 2 units
Cryoprecipitate 8 units

Regular reassessment with Full Blood Count & Coagulation profile every 30-60mins
Consider discussing with Haematologist on-call

Transfusion Recommendations

ROTEIM A10 < 10mm or Fibrinogen < 1.5g/L
Cryoprecipitate 8 units
EXTEM A10 < 40mm or Platelets <80 x 10⁹/L
Platelets 1 adult dose
EXTEM CT > 90 sec or APTT > 50 or INR > 1.5
FFP 4 units
EXTEM ML > 15%
1g Tranexamic Acid

Bleeding controlled, patient stable or deceased
Stop MHP by notifying TMU “28005”
Return unused products to TMU

Urgent baseline bloods
Group & Screen
Full blood count
Coagulation profile
ROTEM
Biochemistry
Venous blood gas

Special Circumstances
Warfarin
10mg Vitamin K
50IU/kg Prothrombinex
Aspirin/Clopidogrel
Platelets 1 adult dose
Bleeding disorder, coagulopathy or NOAC
Contact haematologist

Trauma
1g Tranexamic Acid
within 3hrs
Cryoprecipitate 16units
Obstetric
Haemorrhage
Cryoprecipitate 16units
Immediate release of 4 units Group O Rh (D) negative blood
Or if there is a valid G&S, 4 units Group specific blood

Immediate release of
2 units of pre-thawed
Group AB plasma

Blood components released based on
ROTEM results

What Happens Next?

No ROTEM
MHP Pack 1
RBC 4 units
FFP 2 units

ROTEM
RBC 4 units
Blood components guided by ROTEM
Repeat ROTEM
10mins after blood components given
Major Haemorrhage Protocols

• Testing modalities
  • Standard laboratory tests vs Point of Care testing

• Resuscitation Strategy
  • Fixed ratio transfusion vs Targeted transfusion

• Transfusion Targets and Triggers
  • Fresh products vs Fractionated Products vs Concentrates

• Special Considerations
  • Tranexamic Acid, Fibrinogen replacement
    • ? Recombinant Factor VIIa

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Fixed-Ratio Blood Product Support

MHP Pack 2
- RBC 4 units
- FFP 2 units
- Platelets 1 adult dose

MHP Pack 3
- RBC 4 units
- FFP 2 units
- Cryoprecipitate 8 units

Regular reassessment with Full Blood Count & Coagulation profile every 30-60mins
Consider discussing with Haematologist on-call

REMEMBER
- Temperature > 36°C
- pH > 7.35
- Ca²⁺ > 1.12mmol

Full blood count
Coagulation profile
ROTEM
Biochemistry
Venous blood gas

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Background

• 1985
  • “Massive Transfusion Protocol” first recommended in literature

• 2006
  • Only a few level 1 trauma centres had a MHP in US

• 2007
  • “The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital.”
    • 55% improved survival with high plasma to red cell transfusion ratios

• 2010:
  • 85% of level 1 trauma centres had MHP
Since then...

• Lots of observational and cohort studies including...
• Before-after studies following multiple improvements in care including a 1:1 MHP
  • US military
  • Royal London Hospital
  • Emory Hospital (Paediatric Trauma)
  • University of Texas, Southwest Medical School

• No improvement in mortality
But, What’s the Evidence?
**Objective**—To relate in-hospital mortality to: 1) early transfusion of plasma and/or platelets and 2) time-varying plasma:RBC and platelet:RBC ratios.

**Design**—Prospective cohort study documenting the timing of transfusions during active resuscitation and patient outcomes. Data were analyzed using time-dependent proportional hazards models.

**Setting**—Ten US Level 1 trauma centers.

**Patients**—Adult trauma patients surviving for 30 minutes after admission, transfused at least 1 unit RBC within 6 hours of admission (n=1245, the original study group) and at least 3 total units (of RBC, plasma or platelets) within 24 hours (n=905, the analysis group).

**Main outcome measure**—In-hospital mortality

**Results**—Plasma:RBC and platelet:RBC ratios were not constant over the first 24 hours (p<.001 for both). In a multivariable time-dependent Cox model, increased ratios of plasma:RBC (adjusted hazard ratio, HR=0.31, 95% CI=0.16–0.58) and platelets:RBC (adjusted HR=0.55, 95% CI=0.31–0.98) were independently associated with decreased 6-hour mortality, when hemorrhagic death predominated. In the first 6 hours, patients with ratios < 1:1.2 were 3–4 times more likely to die than patients with ratios ≥1:1. After 24 hours, plasma and platelet ratios were unassociated with mortality, when competing risks from non-hemorrhagic causes prevailed.

**Conclusions**—Higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients transfused at least three units of blood products during the first 24 hours after admission. Among survivors at 24 hours, the subsequent risk of death by day 30 was not associated with plasma or platelet ratios.
Interventions  Blood product ratios of 1:1:1 (338 patients) vs 1:1:2 (342 patients) during active resuscitation in addition to all local standard-of-care interventions (uncontrolled).

Main Outcomes and Measures  Primary outcomes were 24-hour and 30-day all-cause mortality. Prespecified ancillary outcomes included time to hemostasis, blood product volumes transfused, complications, incidence of surgical procedures, and functional status.

Results  No significant differences were detected in mortality at 24 hours (16.7% in 1:1:1 group vs 17.0% in 1:1:2 group; difference, -0.3% [95% CI, -9.5% to 9.8%]; \( P = .12 \)) or at 30 days (22.4% vs 26.1%, respectively; difference, -3.7% [95% CI, -10.2% to 2.7%]; \( P = .26 \)). Exsanguination, which was the predominant cause of death within the first 24 hours, was significantly decreased in the 1:1:1 group (9.2% vs 14.6% in 1:1:2 group; difference, -5.4% [95% CI, -10.4% to -0.5%]; \( P = .03 \)). More patients in the 1:1:1 group achieved hemostasis than in the 1:1:2 group (86% vs 78%, respectively; \( P = .006 \)). Despite the 1:1:1 group receiving more plasma (median of 7 U vs 5 U, \( P < .001 \)) and platelets (12 U vs 6 U, \( P < .001 \)) and similar amounts of red blood cells (9 U) over the first 24 hours, no differences between the 2 groups were found for the 23 prespecified complications, including acute respiratory distress syndrome, multiple organ failure, venous thromboembolism, sepsis, and transfusion-related complications.

Conclusions and Relevance  Among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours. Even though there was an increased use of plasma and platelets transfused in the 1:1:1 group, no other safety differences were identified between the 2 groups.
The Many Faces of Survivor Bias in Observational Studies on Trauma Resuscitation Requiring Massive Transfusion

Anthony M.-H. Ho, MD, FRCP^*^; Jorge E. Zamora, MD, FRCP; John B. Holcomb, MD, FACS; Calvin S. H. Ng, MD, FRCS; Manoj K. Karmakar, MD, FRCA; Peter W. Dion, MD, PhD

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Figure 1. The top panel is a histogram showing the timing of early deaths in the PROMMTT trial. During the initial ~3 hours of emergency department (ED) admission mortality was high and because of delays in initiating FFP and platelet transfusion, FFP:pRBC and platelets:pRBC ratios were low (middle panel) with only a small percentage of patients achieving ratios of >1:2. Type 1 survivor bias is seen when mortality data from patients to the left of line A are included in the analysis. Most of these early deaths are in the low ratio group creating a bias in favor of "1:1:1." To avoid Type 1 survivor bias an investigator might exclude patients to the left of Line A from the analysis, however doing so leaves a cohort that is less coagulopathic and thus is less likely to show benefit from "1:1:1," creating Type 2 survivor bias. The relatively lower death rate to the right of Line A also makes it more difficult to show a beneficial effect of higher FFP and platelet ratios. The bottom panel illustrates Type 3 survivor bias. The solid curves ("before") represent patients before institution of a "1:1:1" protocol, i.e., they were resuscitated in the "traditional" way. The dashed curves ("after") represent patients enrolled after institution of a "1:1:1" transfusion protocol, emphasizing early use of FFP and platelets. A before-after study may include only those patients who had received at least 1 unit of FFP or platelets. In the before group many of the sickest patients are excluded because they died before they received FFP or platelets, resulting in an after group that, comparatively, has a higher probability of death. Survivor bias 3 makes it more difficult to show that early administration of FFP and platelets is beneficial. Data from PROMMTT also show a spike in multi-organ failure 3–30 days after admission amongst survivors (not shown). Since most (~90%) of the survivors will have had high FFP:platelets:pRBC ratios, one may conclude that multi-organ failure is associated with use of FFP:platelets, creating Type 4 survivor bias. FFP, fresh frozen plasma.
Management of traumatic haemorrhage – the European perspective

H. Schöchl, W. Voelckel and C. J. Schlimp

Summary
Trauma-induced coagulopathy represents a life-threatening complication in severely injured patients. To avoid exsanguination, rapid surgical bleeding control coupled with immediate and aggressive haemostatic treatment is mandatory. In most trauma centres, coagulation therapy is established with transfusion of high volumes of fresh frozen plasma. Due to logistic issues, only busy trauma facilities store pre-thawed plasma ready for immediate transfusion. Thus, substantial time delays have been reported between the first unit of red blood cells transfused and the administration of fresh frozen plasma. An alternative for rapid improvement of haemostatic capacity is purified coagulation factor concentrates. They contain a well-defined concentration of coagulation proteins, carry a low risk for transfusion-related lung injury and virus transmission, and are available for immediate use without the need for blood group matching. In some European trauma centres, treatment algorithms have been developed for the administration of coagulation factor concentrates based on visco-elastic test results.
Review Article

Management of traumatic haemorrhage – the US perspective

R. P. Dutton

Clinical Associate, Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois, USA

Summary
As compared with European practice, the American approach to resuscitation from traumatic haemorrhage de-emphasises pre-hospital interventions in favour of rapid transport to definitive care; limits initial surgical interventions under the damage control model; uses crystalloid as the initial fluid of choice; and follows an empiric 1:1:1 approach to transfusion with red cells, plasma and platelets in hemodynamically unstable and actively bleeding patients. The use of bedside visco-elastic testing to guide coagulation support is not as widespread as in Europe, while the early administration of tranexamic acid is more selective.
How I treat patients with massive hemorrhage

Pär I. Johansson, Jakob Stensballe, Roberto Oliveri, Charles E. Wade, Sisse R. Ostrowski and John B. Holcomb
Overall Mortality

Standard lab testing = POC testing = 1:1:1 = 1:1:2
Major Haemorrhage Protocol  
Fiona Stanley Hospital

Critical Bleeding defined by > 3
- HR > 120 bpm
- BP < 90mmHg
- Hb < 90g/L
- INR > 1.5
- pH < 7.25
- Temperature < 35°C

Critically Bleeding Patient with Haemodynamic Instability

Call “S5” to activate “MAJOR HAEMORRHAGE PROTOCOL”
Inform TMU “28005”
Senior clinician to inform TMU if ROTEML is to be used to guide transfusions

No ROTEML
- MHP Pack 1
  - RBC 4 units
  - FFP 2 units

REMEMBER
- Temperature > 36°C
- pH > 7.35
- Ca++ > 1.12 mmol

ROTEML
- RBC 4 units Blood components guided by ROTEML
- Repeat ROTEML 10mins after blood components given

MHP Pack 2
- RBC 4 units
- FFP 2 units
- Platelets 1 adult dose

MHP Pack 3
- RBC 4 units
- FFP 2 units
- Cryoprecipitate 8 units

Regular reassessment with Full Blood Count & Coagulation profile every 30-60mins
Consider discussing with haematologist on-call

Bleeding controlled, patient stable or deceased
Stop MHP by notifying TMU “28005”
Return unused products to TMU

Transfusion Recommendations
- FIBEML A10 < 10mm or Fibrinogen < 1.5g/L
- Cryoprecipitate 8 units
- EXTEM A10 < 40mm or Platelets <80 x 10⁹/L
- Platelets 1 adult dose
- EXTEM CT > 90 sec or APTT > 50 or INR > 1.5
- FFP 4 units
- EXTEM ML > 15%
- 1g Tranexamic Acid

Special Circumstances
- Warfarin
  - 10mg Vitamin K
- 50IU/kg Prothrombinex
- Aspirin/Clopidogrel
  - Platelets 1 adult dose
- Bleeding disorder, coagulopathy or NOAC
  - Contact haematologist

Trauma
- 1g Tranexamic Acid within 3hrs
- Cryoprecipitate 16 units
- Obstetric
- Haemorrhage
- Cryoprecipitate 16 units

Anastazia Keegan 2016
Major Haemorrhage Protocols

• Testing modalities
  • Standard laboratory tests vs Point of Care testing

• Resuscitation Strategy
  • Fixed ratio transfusion vs Targeted transfusion

• Transfusion Targets and Triggers
  • Fresh products vs Fractionated Products vs Factor Concentrates

• Special Considerations
  • Tranexamic Acid, Fibrinogen replacement
    • ? Recombinant Factor VIIa
• Senior clinician can react to laboratory results and request blood products to correct coagulopathy

• Transfusion medicine may also offer this advise

• Discuss with haematologist

Transfusion Recommendations
FIBTEM A10 < 10mm or Fibrinogen < 1.5g/L
Cryoprecipitate 8 units

EXTEM A10 < 40mm or Platelets <80 x 10⁹/L
Platelets 1 adult dose

EXTEM CT > 90 sec or APTT > 50 or INR > 1.5
FFP 4 units

EXTEM ML > 15%
1g Tranexamic Acid
Coagulation Factor Replacement

Fresh Frozen Plasma
• Manufactured from whole blood or apheresis donation
• Contains all of the coagulation Factors
• 250-300mls
• Needs to be defrosted (30mins)
• Association with TRALI/TACO

COST: $310/unit

Prothrombinex-VF
• Manufactured by CSL-Behring from human plasma
• FII, IX, X (trivial FV, VII) concentrate
• Dose: 15-50 IU/kg
• Peak plasma concentration 5mins
• No evidence for use of Prothrombinex in massive haemorrhage

COST: $275/500 IU
### Coagulation Factor Replacement

#### Cryoprecipitate
- Manufactured from whole blood or apheresis donation
- Contains FVIII, Fibrinogen, FXIII, VWF and Fibronectin
- Fibrinogen: 420 ± 120 mg/unit
- Standard issue: 8-10 units
- Needs to be defrosted (10mins)

**COST:** $175-$300/unit

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#### Fibrinogen Concentrate
- Manufactured by CSL Behring from international donors
- Concentrated fibrinogen
- Dosing: 1g vials
- Only approved for congenital afibrinogenaemia and dysfibrinogenaemia in Australia

**COST:** $750/1g
Major Haemorrhage Protocols

• Testing modalities
  • Standard laboratory tests vs Point of Care testing

• Resuscitation Strategy
  • Fixed ratio transfusion vs Targeted transfusion

• Transfusion Targets and Triggers
  • Fresh products vs Fractionated Products vs Factor Concentrates

• Special Considerations
  • Tranexamic Acid, Fibrinogen replacement
  • ? Recombinant Factor VIIa
Major Haemorrhage Protocol
Fiona Stanley Hospital

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- Temperature < 35°C

**Critically Bleeding Patient with Haemodynamic Instability**

**Call “S5” to activate “MAJOR HAEMORRHAGE PROTOCOL”**

**Inform TMU “28005”**

Senior clinician to inform TMU if ROTEM is to be used to guide transfusions

**No ROTEM**

- MHP Pack 1
  - RBC 4 units
  - FFP 2 units

**ROTEN**

- RBC 4 units
  - Blood components guided by ROTEM
- Repeat ROTEM
- 10mins after blood components given

**REMEMBER**
- Temperature > 36°C
- pH > 7.3
- Ca²⁺ > 1.12 mmol

- MHP Pack 2
  - RBC 4 units
  - FFP 2 units
  - Platelets 1 adult dose

- MHP Pack 3
  - RBC 4 units
  - FFP 2 units
  - Cryoprecipitate 8 units

**Regular reassessment** with Full Blood Count & Coagulation profile every 30-60 mins

Consider discussing with haematologist on-call

- Bleeding controlled, patient stable or deceased
- Stop MHP by notifying TMU “28005”
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**Transfusion Recommendations**
- FIBTEM A10 < 10mm or Fibrinogen < 1.5g/L
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- EXTEM ML > 15%
- 1g Tranexamic Acid

**Special Circumstances**
- Warfarin
  - 10mg Vitamin K
  - 50U/kg Prothrombinex
  - Aspirin/Clopidogrel
  - Platelets 1 adult dose

- Bleeding disorder, coagulopathy or NOAC
- Contact haematologist

**Trauma**
- 1g Tranexamic Acid within 3hrs
- Cryoprecipitate 16 units
- Obstetric
- Haemorrhage
- Cryoprecipitate 16 units

Anastazia Keegan 2016
Special Circumstances

- Remember to think about special circumstances
  - Modify management early
  - Communicate with Transfusion Medicine

- History of congenital or acquired bleeding disorders including NOACS
  - Discuss with haematologist

Special Circumstances

Warfarin
10mg Vitamin K
50IU/kg Prothrombinex

Aspirin/Clopidogrel
Platelets 1 adult dose

Bleeding disorder, coagulopathy or NOAC
Contact haematologist
**Hyperfibrinolysis**

**Trauma-Induced Coagulopathy**

**Dilutional Coagulopathy**

- **1g Tranexamic Acid**
  - Intravenous bolus within 3 hours of trauma
    - CRASH 2 Study

- **16 Units of Cryoprecipitate**
  - Early and aggressive management of Trauma-Induced Coagulopathy
Pathogenesis of Coagulopathy in Transfusions in Trauma

Severe trauma → Bleeding

Coagulopathy

Acidosis

Tissue hypoxia

Hypothermia

Colloid and crystalloid infusion

Massive RBC transfusion

Dilution of coagulation factors and platelets
Trauma-Induced Coagulopathy

• Upregulation of thrombomodulin
  • Autoheparinisation
  • Activation of Protein C
  • Depletion of Factor V
    • Uncontrolled t-PA
    • Hyperfibrinolysis

• Reduced fibrinogen with reduction in fibrin clot
“Damage Control Resuscitation”

• Permissive hypotension
• Minimise crystalloid resuscitation
• Activation of the Major Haemorrhage Protocol
  – Immediate blood and blood product resuscitation
  – Early Tranexamic acid
• Prevent the “Lethal Triad of Trauma”
  – Coagulopathy
  – Acidosis
  – Hypothermia
Obstetric Haemorrhage
Major Haemorrhage Protocol

HYPERFIBRINOLYSIS

• 16 UNITS of CRYOPRECIPITATE
Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia (Review)

Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C
Main results

Twenty-nine RCTs were included: 28 were placebo-controlled, double-blind RCTs and one compared different doses of rFVIIa. In the ‘Risk of bias’ assessment, most studies were found to have some threats to validity although therapeutic RCTs were found to be less prone to bias than prophylactic RCTs.

Sixteen trials involving 1361 participants examined the prophylactic use of rFVIIa; 729 received rFVIIa. There was no evidence of mortality benefit (risk ratio (RR) 1.04; 95% confidence interval (CI) 0.55 to 1.97). There was decreased blood loss (mean difference (MD) -297 mL; 95% CI -416 to -178) and decreased red cell transfusion requirements (MD -261 mL; 95% CI -367 to -154) with rFVIIa treatment; however, these values were likely overestimated due to the inability to incorporate data from trials (four RCTs in the outcome of blood loss and three RCTs in the outcome of transfusion requirements) showing no difference of rFVIIa treatment compared to placebo. There was a trend in favour of rFVIIa in the number of participants transfused (RR 0.85; 95% CI 0.72 to 1.01). However, there was a trend against rFVIIa with respect to thromboembolic adverse events (RR 1.35; 95% CI 0.82 to 2.25).

Thirteen trials involving 2929 participants examined the therapeutic use of rFVIIa; 1878 received rFVIIa. There were no outcomes where any observed advantage or disadvantage of rFVIIa over placebo could not have been observed by chance alone. There was a trend in favour of rFVIIa for reducing mortality (RR 0.91; 95% CI 0.78 to 1.06). However, there was a trend against rFVIIa for increased thromboembolic adverse events (RR 1.14; 95% CI 0.89 to 1.47).

When all trials were pooled together to examine the risk of thromboembolic events, a significant increase in total arterial events was observed (RR 1.45; 95% CI 1.02 to 2.05).

Authors’ conclusions

The effectiveness of rFVIIa as a more general haemostatic drug, either prophylactically or therapeutically, remains unproven. The results indicate increased risk of arterial events in patients receiving rFVIIa. The use of rFVIIa outside its current licensed indications should be restricted to clinical trials.
So, the Summary of the Evidence...

- MHP improve outcomes in patients with critical bleeding who require massive transfusions

- Standard lab testing = POC testing = 1:1:1 = 1:1:2

  - Use tranexamic acid in trauma (early)

- No indication for off-label use of Factor VIIa
KEEP CALM AND ACTIVATE THE MAJOR HAEMORRHAGE PROTOCOL
Description of contents & return instructions

Platelets stored here at Room Temperature

Cryo stored here at Room Temperature

Red cells & FFP stored inside at 4°C