Current Evidence based management of Massive Haemorrhage

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Summary

- A small proportion (4%) need an aggressive approach to transfusion.
- Systems that include plasma and platelets improve outcome.
- The key component in plasma is fibrinogen.
- The challenge is to develop systems that deliver fibrinogen rapidly enough to these patients.
- The place of Tranexamic Acid in Trauma is evolving, and is being studied locally.

- Unless we include POC monitoring of coagulopathy we risk replacing exsanguination with thrombosis.
No Transfusion | Focused Tx | DCR

10 units RBC in 4 hrs

10 units RBC in 24 hrs
Changes in causes of death

Haemorrhage as a cause of death has fallen from 32% to 8%
Has improved injury care impacted on the trimodal pattern of death?

Epidemiology of Trauma Deaths: A Reassessment
Susaia, Angela MD; Moore, Frederick A. MD; Moore, Ernest E. MD; Moser, Kathe S. PRA; Brennan, Regina RN, MS; Read, Robert A. MD; Pors, Peter T. MD

Abstract

Objective: Recognizing the impact of the 1977 San Francisco study of trauma deaths in trauma care, our purpose was to reassess those findings in a contemporary trauma system.

Figure 3. Temporal distribution of trauma deaths caused by CNS injuries and exsanguination, excluding individuals who were found dead by police.
WHEN DOES THE COAGULOPATHY OF TRAUMA DEVELOP?
Presence of coagulopathy in ED

- 25% of trauma patients
- 3 - 4 times more likely to die
- 8 times more likely to die in the next 24 hrs
  - Maegele; Injury 2007 38: 298-304

- Abnormal APTT OR 4.3
- Abnormal PT OR 1.4
- Abnormal thrombomodulin OR 2.5
- Low protein C OR 6.2
Transfusion requirements

- Longer ICU Stay
- Increased incidence of renal failure and MOF

- In first 24 hrs of admission
  - With hypoperfusion
    - If APPT > 1.5 times normal 10 units RBCS
    - If APPT normal 2 units RBCS
Acute Traumatic Coagulopathy
The coagulopathy is related to

SHOCK plus

TISSUE INJURY.

Brohi, J Trauma 2003; 54 1127-1130
Trauma Induced Coagulopathy

- Usually has an adequate Thrombin burst
- Fibrinogen levels are reduced
- Fibrin laydown and cross-bridging is impaired
- tPA and Fibrinolysis are increased
- Platelet dysfunction effect in “severe” trauma
Early hemostatic responses to trauma identified with hierarchical clustering analysis

Journal of Thrombosis and Haemostasis 10.1111/jth.12919
Early hemostatic responses to trauma identified with hierarchical clustering analysis

**A**

<table>
<thead>
<tr>
<th>Injury, shock severity, and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild injury (ISS 0–15)</td>
</tr>
<tr>
<td>Severe injury (ISS 16–24)</td>
</tr>
<tr>
<td>Profound injury (ISS 25–75)</td>
</tr>
<tr>
<td>Shock (Base excess &lt;=-6 meq/L)</td>
</tr>
<tr>
<td>72 h mortality</td>
</tr>
</tbody>
</table>

% Subjects meeting criteria

1 2 3
Cluster

**C**

8-h transfusion requirements

- Packed red blood cells
- Fresh frozen plasma
- Platelet concentrate
- Cryoprecipitate

% Subjects receiving blood product

1 2 3
Cluster

*Journal of Thrombosis and Haemostasis*

pages 978-988, 9 MAY 2015
Online First

The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study

Comparative Effectiveness of a Time-Varying Treatment With Competing Risks

John B. Holcomb, MD; Deborah J. del Junco, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Mitchell J. Cohen, MD; Martin A. Schreiber, MD; Louis H. Alarcon, MD; Yu Bai, MD, PhD; Karen J. Brasci, MD, MPH; Eileen M. Bulger, MD; Bryan A. Cotton, MD, MPH; Nena Matijevic, PhD; Peter Muskat, MD; John G. Myers, MD; Herb A. Philan, MD, MScS; Christopher E. White, MD; Jiajie Zhang, PhD; Mohammad H. Rahbar, PhD, for the PROMMTT Study Group

- 10 US Trauma centres
- 906 patients > 3 units pRBC (of 35,000 admissions)
- Within first 24 hrs mortality from bleeding reduced 3-4 times with 1:1 ratio
- NO difference in outcome after 24hrs
Do you survive because of early plasma, or because you survive you get plasma?
Time matters in 1:1 resuscitations: Concurrent administration of blood:plasma and risk of death

Stephanie A. Savage, MD, Ben L. Zarzaur, MD, Martin A. Croce, MD, and Timothy C. Fabian, MD, Memphis, Tennessee

Figure 1. HRs for mortality in CAT+ patients.
Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma
The PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachel A. Callcut, MD, MSPH; Mitchell Jay Cohen, MD; Brian A. Cotton, MD, MPH; Timothy C. Fabian, MD; Kenji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Peter Mushat, MD; Terence O’Keefe, MBChB, MSPH.

24-h Mortality

30-d Mortality

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study

Jonathan J. Morrison, MB ChB, MRCS; Joseph J. Dubose, MD; Todd E. Rasmussen, MD; Mark J. Midwinter, BMedSci, MD, FRCS

Figure 2. Percentage of patients with hypocoagulopathy on admission to the emergency department (ED) and then the intensive care unit (ICU) following the initial operation. Coagulation data were available for 462 patients in the overall cohort and 155 patients in the groups that received massive transfusion. TXA indicates tranexamic acid. *P < .05.

Figure 4. Kaplan-Meier survival curve of the massive transfusion group receiving tranexamic acid (TXA) or no TXA. P = .004, Mantel-Cox log-rank test.
The PATCH trial

- Prospective, multicenter, double blind, randomised trial of TXA vs placebo in patients with severe trauma and a high risk of death
- Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage Trial
- ANZICS clinical trials group
- Many sites in Australia and New Zealand taking part
Sites

- New Zealand
  - Auckland Hospital
  - Middlemore Hospital
  - Waikato Hospital
  - Hawkes Bay Hospital
  - Wellington Hospital
  - Christchurch Hospital
  - Dunedin Hospital
- Australia
  - Victoria
  - Queensland
  - South Australia
  - Western Australia
Practical aspects

• Patients will already be randomised
• ‘Hospital ampoule’
  – Infuse over 8 hours
  – Can be added to saline, PL148 or glucose
• All other treatment is as ‘per usual’
• TXA may be administered if clinician feels very strongly that it must be administered
  – We ask that it is preferably not
• Plan to start in Auckland on 16 November
WHEN DO YOU ACTIVATE A MTP?
## Initiating the Massive Transfusion Protocol

<table>
<thead>
<tr>
<th></th>
<th>ABC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>TASH&lt;sup&gt;2&lt;/sup&gt;</th>
<th>McLauchlin&lt;sup&gt;3&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>ED pulse</td>
<td>&gt; 120</td>
<td>&gt; 120</td>
<td>&gt; 105</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>&lt; 90</td>
<td>&lt; 100</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>BE</td>
<td></td>
<td>-2 to -10</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td>&lt; 7.2</td>
</tr>
<tr>
<td>Hb</td>
<td></td>
<td>7 - 12</td>
<td>&lt; 9.6</td>
</tr>
<tr>
<td>FAST</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Penetrating</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable pelvic # or femoral #</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ‘newest” MTP

TXA is suggested

Blood Bank Responsibilities

- Ensure X-match sample processed ASAP after O-neg release
- Notify NZBS Medical Officer after issuing MTP Box One
- Thaw next box in advance and await request
- Ensure supply of platelets

Contacts

- Blood Bank - Ext 24015
- Coagulation Lab - Ext 7572
- Level 8 Anaesthetist - 021 496 374

REQUEST, DELIVER AND TRANSFUSE AS BELOW:

MTP BOX ONE
2 Whole Blood or 2U RBC
and 2U FFP

MTP BOX TWO
4 RBC
4 FFP
3U Cryoprecipitate

MTP BOX THREE
4 RBC
4 FFP
1U Platelets

MTP BOX FOUR
4 RBC
4 FFP

Check Coags / Platelets /FBC
ABGs / Ca**

No fVIIa

Repeat every 30 min

Ring Blood Bank to Activate Massive Transfusion Protocol

Cryo comes before platelets
**TEG ALGORITHM FOR MANAGEMENT OF BLEEDING PATIENTS**

**Kaolin TEG**

**R time 10-14**
- R time >14
  - Heparin effect possible? Check Heparinase TEG
  - Difference in R time > 2min
    - Give Protamine 25-50mg

**R time >14**
- MA <49 or α <52
  - Measure Functional Fibrinogen
  - Factor Deficiency
    - Give 2 units FFP
  - Factor Deficiency
    - Give 4 units FFP

**Ly30 >8**
- Fibrinolysis
  - Tx A 10-20mg/kg

**MA <49 FFMA <7**
- Low Fibrinogen
  - Give 4u Cryo (or 4g Fibrinogen)

**MA <49 FFMA 7-14**
- Low Fibrinogen
  - Give 2u Cryo (or 2g Fibrinogen)

**MA 45-49 FFMA >14**
- Low Platelets
  - Give I unit platelets

**MA <45 FFMA >14**
- Low Platelets
  - Give 2 units platelets
Focus on reducing bleeding not transfusion

CME

Fibrinogen and Hemostasis: A Primary Hemostatic Target for the Management of Acquired Bleeding

Jerrold H. Levy, MD, FAHA, Fania Szlamo, MMSc, Kenichi A. Tanaka, MD, and Roman M. Sniecienski, MD
Does mortality drop with Fibrinogen concentrate?

2012;20:15–25
## SOURCES OF FIBRINOGEN

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen Content</th>
<th>Thaw Time Delay</th>
<th>Factors Present</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FFP</strong></td>
<td>1.6G/L</td>
<td>30 min. + Transport</td>
<td>Fibrinogen (I) II, VII, IX, X, XII [V &amp; VIII 65% (N)]</td>
<td>Weak TACO TRALI immunomodulation</td>
</tr>
<tr>
<td><strong>Cryoprecipitate</strong></td>
<td>1.3G/150ml</td>
<td>30 min. + Transport</td>
<td>Fibrinogen (I) vWF, VIII XIII fibronectin</td>
<td>Availability no viral inactivation</td>
</tr>
<tr>
<td><strong>Fibrinogen Concentrate</strong></td>
<td>1.0G/50ml</td>
<td>NIL</td>
<td>Fibrinogen (I)</td>
<td>Cost 20% greater than cryoprecipitate</td>
</tr>
</tbody>
</table>
Auckland MTP: fibrinogen

Fibrinogen Pre-Post
95% CI for the Mean
Electron microscopic scan of a ×2000 magnified blood clot.

- **fibTEM >10mm**  
  - undiluted
  - 65% haemodiluted

- **Fibrinogen > 1.5-2.0 g/L**
  - Post fibrinogen administration

Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial

N. Curry¹,², C. Rourke², R. Davenport², S. Beer¹, L. Pankhurst³, A. Dearv³.

**Fig 2** Comparison of Mean Fibrinogen Concentrations (Standard Deviation) between Study Arms for the Duration of the Trial. Changes of Claus fibrinogen concentrations were compared using a two way ANOVA with repeated measures for patients in each arm of the trial. No evidence of a difference between changes in mean Claus fibrinogen concentrations at 24 h and 72 h and the arm of the trial.
Higher fibrinogen concentrations for reduction of transfusion requirements during major paediatric surgery: A prospective randomised controlled trial

T. Haas1,*, N. Spielmann1, T. Restin2, B. Seifert3, G. Henze1, J. Obwegeser4, K. Min5, D. Jeszenszky6, M. Weiss1, and M. Schmugge7

Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial†

**Team Leader Responsibilities**

- Team leader should be a trauma team member
- Notify Coag Lab and send Coag requests on the Labplus Urgent form (orange border)
- Activate protocol by ringing Blood Bank (ext 24015) and say “I am activating the “Code Crimson MTP”
- Call for each box as required
- Make a decision to cease MTP and contact Blood Bank

**Blood Bank Responsibilities**

- Ensure X-match sample processed ASAP after O-neg release
- Notify NZBS Medical Officer after issuing MTP Box Four
- Thaw next box in advance and await request
- Ensure supply of platelets

**Additional treatment thresholds**

- If PR >1.5 or APTT >40 consider additional 4 units FFP
- If fibrinogen <1g/L consider additional 3U Cryoprecipitate
- If platelets <75 x10^9/L consider additional one pack platelets
- If ionized Ca++ <1mmol/L give 10mls Calcium

**Massive bleeding (ABC Score ≥ 2/4)**

- Consider Tranexamic acid 1g
- Ensure delivery of X-match specimen to Blood Bank

**Give 3 Units O-neg or type specific RBC**

- Ring Blood Bank to Activate Code Crimson MTP

**REQUEST, DELIVER AND TRANSFUSE AS BELOW:**

- MTP BOX ONE: 2U RBC and 4G Fibrinogen concentrate
- MTP BOX TWO: 4 RBC 4 FFP 3U Cryoprecipitate
- MTP BOX THREE: 4 RBC 4 FFP 1U Platelets
- MTP BOX FOUR: 4 RBC 4 MPs 3U Cryoprecipitate

- Check Coags / TEG/Platelets /FBC ABGs / Ca++
- Check TEG/Coags / Platelets /FBC ABGs / Ca++
- Repeat every 30 min

- and alternate 3 & 4...
Component Usage

**Boxplot of Red Cells by Year**

- Year: 2006 to 2015
- Data range: 1100 to 2000

**Boxplot of Fresh Frozen Plasma**

- Year: 2006 to 2015
- Data range: 200 to 700

**I Chart of Cryoprecipitate**

- Individual Value: Jan-06 to Mar-15
- Data range: 0 to 200
- UCL = 151.0
- LCL = 21.8

**Boxplot of Platelets**

- Year: 2006 to 2015
- Data range: 200 to 550

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Auckland District Health Board
Trauma flowsheet in Innsbruck

Algorithm for treating bleeding in patients with trauma-induced coagulopathy:

1. **Optimize preconditions**
   - Temperature > 36°C
   - pH > 7.2
   - Calcium >1 mmol/L
   - Hematocrit > 24%

2. **Run ROTEM (EXTEM, INTEM, FIBTEM, APTEM)**
   - If EXTEM CT > APTEM CT
     - **Treat fibrinolysis**
       - TXA 15-40 mg/kg BW
   - If FIBTEM CA10 < 10 mm
     - Increase FIBTEM CA10 to 10-12 mm
       - Fibrinogen concentrate 10-20 g
     - (Cryoprecipitate, FFP)
   - If EXTEM CT > 42 sec
     - Increase platelet count to 2-10 x 10^9/L
       - Platelet concentrate
   - If EXTEM CA10 < 40 mm
     - Treat immediately
       - TXA 15-40 mg/kg BW
     - Fibrinogen concentrate 6-8 and FFP 50-100 U/kg BW
     - (Cryoprecipitate, FFP [high dose])
     - Platelet concentrate (increase platelet count to 3 x normal)

- **ROTEM may also identify:**
  - Potential heparin exposure (e.g., cell-saver bleed)
    - HEPTEM CT < INTEM CT
      - **Treat heparin effect**
        - Protamine 1000-2000 U
  - Cost instability not related to hyperfibrinolysis
    - EXTEM ML > 15% and APTEM ML > 15%
      - Consider Factor XIII 150 U
The components of damage control resuscitation

- Permissive hypotension
- Haemostatic resuscitation
- Damage control surgery

598 patients with penetrating torso trauma and systolic BP < 90
Arrival systolic BP averaged 72 mmHg in ‘limited’ resusc, 79mm in ‘standard’
Standard resuscitation vs Limited resuscitation (until operating theatre)
Limited resuscitation: 30% mortality and 23% complication rate
Standard Resuscitation: 38% mortality (p=0.04) and 30% complication rate
Hypotensive Resuscitation Strategy Reduces Transfusion Requirements and Severe Postoperative Coagulopathy in Trauma Patients With Hemorrhagic Shock: Preliminary Results of a Randomized Controlled Trial

C. Anne Morrison, MD, MPH, Matthew M. Carrick, MD, Michael A. Norman, MD, Bradford G. Scott, MD, Francis J. Welsh, MD, Peter Tsai, MD, Kathleen R. Liscum, MD, Matthew J. Wall, Jr., MD, and Kenneth L. Mattax, MD

1. Diagram of the patient flow from left to right.

Figure 3. Kaplan–Meier survival curves.
Liver laceration

\[ T = 34.6 \text{ degrees} \]
<table>
<thead>
<tr>
<th>Fluid Name</th>
<th>Total Volume</th>
</tr>
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<tbody>
<tr>
<td>RBC</td>
<td>5046</td>
</tr>
<tr>
<td>FFP</td>
<td>2168</td>
</tr>
<tr>
<td>Platelets pooled</td>
<td>553</td>
</tr>
<tr>
<td>Plasmalyte</td>
<td>2500</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>306</td>
</tr>
</tbody>
</table>
Liberal Versus Restricted Fluid Resuscitation Strategies in Trauma Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Observational Studies*

Chih-Hung Wang, MD; Wen-Han Hsieh, MS; Hao-Chang Chou, MD; Yu-Sheng Huang, MD; Jen-Hsiang Shen, MS; Yee Hui Yeo, MS; Huai-En Chang, MS; Shyr-Chyr Chen, MD, MBA; Chien-Chang Lee, MD, MSc
Restrictive Fluids are the key

Figure 2. A: Forest plot for randomized controlled trials. Comparison of the effects of liberal versus restricted fluid resuscitation on overall mortality, expressed as risk ratio (RR) and 95% CI. B: Forest plot for random-
Auckland District Health Board

Focused Tx
No Transfusion

ISS
Shock

DCR

MTP

Tranexamic Acid

Red Cells

Red Cells plus FFP

Add cryo or fibrinogen

ISS >16
Lactate >2 x normal
PT >1.5
Pulse >120
Systolic <90
Ongoing non surgical bleeding.

?PCC
?Factor VIIa
?Factor XIII

ISS >16
Lactate >2 x normal
PT >1.5
Pulse >120
Systolic <90
Ongoing non surgical bleeding.
Complex patients, sensible answers
Finding the correct pathway to difficult medical and ethical problems

Our keynote speakers

Assist. Prof. Thomas Weiser
Stanford University, California, USA

Prof. W. Scott Beattie
University of Toronto, Canada

Saturday
12 March 2016

School of Medicine
The University of Auckland
Grafton, Auckland, New Zealand

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