The Role of Tranexamic Acid (TXA) in Massive Transfusion Protocol

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Objectives

TXA:

- Understand the various models of massive transfusion protocols (MTPs)
- Review the published CRASH-2 data
- Evaluate the role of tranexamic acid within a massive transfusion protocol
Definitions of Massive Transfusion

- Blood loss rate of 150 mL/min
- Replacement of 0.5 TBV over 3 hours
- Replacement of 1 TBV over 24 hours
- Transfusion of >10 RBC units over 24 hours or from time of ED admissions to ICU transfer
- Transfusion of >20 RBC units in the course of a hospital admission
Lab parameters and transfusion triggers guide massive transfusion management.

Prearranged delivery system of blood products in various mixtures of RBC:plasma:platelets:cryoprecipitate to stabilize bleeding event.
Surgery, Anesthesia, Clinical Team Response: Treatment of Shock

Uncontrolled Hemorrhage
- e.g. SBP < 90mmHg Despite 3 ½ Liter Crystalloid (50mL/kg)
- e.g. EBL > 150 mL/minute (see other definitions of massive bleeding)
- e.g. pH<7.1; body temperature <34°C; ISS > 25

Adult Massive Transfusion Protocol (MTP) Activation
Attending M.D. or one designated personnel (e.g. Charge Nurse) notifies Blood Bank directly

Blood Bank Response
- First cooler with 4 units of O-negative pRBC available for pickup and begin thawing 2 units of AB FFP
- Confirmation with clinical team to:
  - Establish Pt. Identifiers
  - Expect appropriately labelled type & crossmatch specimen and the subsequent issuance of type specific blood products

Surgery, Anesthesia, Clinical Team Response: Continued Treatment of Shock

MTP
Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients

Beth H. Shaz, Christopher J. Dente, Jeffrey Nicholas, Jana B. MacLeod, Andrew N. Young, Kirk Easley, Qiang Ling, Robert S. Harris, and Christopher D. Hillyer

Pre-MTP group
The pre-MTP group was created by querying the prospectively entered trauma registry and identifying all patients in the 2 years before the institution of the MTP (February 1, 2005-January 31, 2007) who received 10 or more units of RBCs in the first 24 hours of their hospital stay.

<table>
<thead>
<tr>
<th>Package</th>
<th>RBCs</th>
<th>Plasma</th>
<th>PLTs</th>
<th>Cryoprecipitate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>6 units</td>
<td>6 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 units</td>
<td>6 units</td>
<td>1 apheresis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 units</td>
<td>6 units</td>
<td></td>
<td>20 units</td>
</tr>
<tr>
<td>3</td>
<td>6 units</td>
<td>6 units</td>
<td>1 apheresis</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6 units</td>
<td>6 units</td>
<td></td>
<td>10 units</td>
</tr>
<tr>
<td>5</td>
<td>6 units</td>
<td>6 units</td>
<td>1 apheresis</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6 units</td>
<td>6 units</td>
<td></td>
<td>10 units</td>
</tr>
</tbody>
</table>

Figure 5

Predicted probability of death in patients undergoing massive transfusion according to FFP:PRBC ratio at 6 hours post injury. The lowest predicted mortality probability, (0.35, trendline), was found to correlate with transfusion ratios in the range of 1:2 to 1:3.

When Penetrating trauma leading to operating room death were excluded, predicted probability of death in patients undergoing massive transfusion according to FFP: PRBC ratio demonstrated strengthening of the U shaped curve, with the predicted probability of mortality decreasing to 0.2 (trend line) over the transfusion ratio of 1:2 to 1:3.
“Current data indicate that the early identification of coagulopathy and its treatment with RBCs, plasma, and platelets in a 1:1:1 unit ratio achieved with the use of fresh RBCs, thawed plasma, and platelets; limited use of crystalloids; and accompanied with rapid hemorrhage control may improve survival in the uncommon patient who presents with severe traumatic injury and life-threatening bleeding.”

Holcomb JB. Optimal use of blood products in severely injured trauma patients. ASH 2010; 465-469.

“Finally, the potential adverse effects of FFP administration must be considered, as we…have shown that FFP and platelets, as well as RBC are independent risk factors for the development of transfusion associated lung injury (TRALI) and multiple organ failure (MOF). In sum, although most civilian transfusion guidelines embrace liberal FFP administration in acutely injured patients with massive blood loss, the ideal ratio for this patient population remains to be analyzed.”


- TEG implemented after internal review found 10% of patients with suboptimal transfusion therapy (University of Copenhagen, Denmark)

- TEG impacts:
  - 97% predictability in identifying a surgical cause of bleeding in postoperative patients
  - 10% of MTP patients had hyperfibrinolysis
  - 45% of MTP patients were hypercoagulable
  - Reduction of suboptimal transfusion from 10% to <3%
CRASH-2: Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage 2
Tranexamic Acid (TXA)

CRASH-2 Study

Figure 1: Trial profile


<table>
<thead>
<tr>
<th>Time from injury (h)</th>
<th>Tranexamic acid allocated</th>
<th>Placebo allocated</th>
<th>Risk ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>509/3747 (13.6%)</td>
<td>581/3704 (15.7%)</td>
<td>0.87 (0.75-1.00)</td>
</tr>
<tr>
<td>&gt;1–&lt;3</td>
<td>463/3037 (15.2%)</td>
<td>528/2996 (17.6%)</td>
<td>0.87 (0.75-1.00)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>491/3272 (15.0%)</td>
<td>502/3362 (14.9%)</td>
<td>1.00 (0.86-1.17)</td>
</tr>
</tbody>
</table>

χ²=4.411; p=0.11

<table>
<thead>
<tr>
<th>Systolic blood pressure (mm Hg)</th>
<th>Tranexamic acid allocated</th>
<th>Placebo allocated</th>
<th>Risk ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>702/6878 (10.2%)</td>
<td>736/6761 (12.9%)</td>
<td>0.94 (0.82-1.07)</td>
</tr>
<tr>
<td>76–89</td>
<td>280/1609 (17.5%)</td>
<td>312/1689 (18.5%)</td>
<td>0.94 (0.78-1.14)</td>
</tr>
<tr>
<td>≤75</td>
<td>478/1562 (30.6%)</td>
<td>562/1599 (35.1%)</td>
<td>0.87 (0.76-0.99)</td>
</tr>
</tbody>
</table>

χ²=1.345; p=0.51

<table>
<thead>
<tr>
<th>GCS</th>
<th>Tranexamic acid allocated</th>
<th>Placebo allocated</th>
<th>Risk ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe (3–8)</td>
<td>796/1789 (44.5%)</td>
<td>860/1830 (47.0%)</td>
<td>0.95 (0.86-1.04)</td>
</tr>
<tr>
<td>Moderate (9–12)</td>
<td>219/1349 (16.2%)</td>
<td>249/1344 (18.5%)</td>
<td>0.88 (0.70-1.09)</td>
</tr>
<tr>
<td>Mild (13–15)</td>
<td>447/6915 (6.5%)</td>
<td>502/6877 (7.3%)</td>
<td>0.88 (0.75-1.04)</td>
</tr>
</tbody>
</table>

χ²=1.387; p=0.50

<table>
<thead>
<tr>
<th>Injury type</th>
<th>Tranexamic acid allocated</th>
<th>Placebo allocated</th>
<th>Risk ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt</td>
<td>1134/6788 (16.7%)</td>
<td>1233/6817 (18.1%)</td>
<td>0.92 (0.83-1.02)</td>
</tr>
<tr>
<td>Penetrating</td>
<td>329/3272 (10.1%)</td>
<td>380/3250 (11.7%)</td>
<td>0.86 (0.72-1.03)</td>
</tr>
</tbody>
</table>

χ²=0.791; p=0.37

<table>
<thead>
<tr>
<th>All patients</th>
<th>Tranexamic acid better</th>
<th>Tranexamic acid worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-sided</td>
<td>p=0.0035</td>
<td></td>
</tr>
<tr>
<td>1463/10060 (14.5%)</td>
<td>1613/10067 (16.0%)</td>
<td>0.91 (0.85-0.97)*</td>
</tr>
</tbody>
</table>

Figure 3: All-cause mortality by subgroups
GCS= Glasgow Coma Score. *95% CI.

<table>
<thead>
<tr>
<th>Item</th>
<th>Tanzania</th>
<th>India</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ICU hospital stay ($)*</td>
<td>135,183</td>
<td>213,435</td>
<td>3,272,416</td>
</tr>
<tr>
<td>TXA</td>
<td>134,641</td>
<td>212,315</td>
<td>3,255,244</td>
</tr>
<tr>
<td>No TXA</td>
<td>17,483</td>
<td>19,550</td>
<td>30,830</td>
</tr>
<tr>
<td>TXA administration cost ($)*</td>
<td>18,025</td>
<td>20,670</td>
<td>48,002</td>
</tr>
<tr>
<td>Overall incremental cost ($)*</td>
<td>13,079</td>
<td>18,176</td>
<td>24,162</td>
</tr>
<tr>
<td>Life years gained discounted*</td>
<td>12,707</td>
<td>17,861</td>
<td>23,407</td>
</tr>
<tr>
<td>Incremental life year saved*</td>
<td>372</td>
<td>315</td>
<td>755</td>
</tr>
<tr>
<td>Incremental cost per life year saved ($)</td>
<td>48</td>
<td>66</td>
<td>64</td>
</tr>
</tbody>
</table>

* per 1,000 patients.
doi:10.1371/journal.pone.0018987.t002
Massive transfusion protocol (MTP) template

The information below, developed by consensus, broadly covers areas that should be included in a local MTP. This template can be used to develop an MTP to meet the needs of the local institution’s patient population and resources.

Senior clinician determines that patient meets criteria for MTP activation

Baseline:
Full blood count, coagulation screen (PT, INR, APTT, fibrinogen), biochemistry, arterial blood gases

Notify transfusion laboratory *(insert contact no.)* to: ‘Activate MTP’

Laboratory staff
- Notify haematologist/transfusion specialist
- Prepare and issue blood components as requested
- Anticipate repeat testing and blood component requirements
- Minimise test turnaround times
- Consider staff resources

Haematologist/transfusion specialist
- Liaise regularly with laboratory and clinical team
- Assist in interpretation of results, and advise on blood component support

Senior clinician
- Request:
  - 4 units RBC
  - 2 units FFP
- Consider:
  - 1 adult therapeutic dose platelets
  - tranexamic acid in trauma patients
- Include:
  - cryoprecipitate if fibrinogen < 1 g/L
  - Or locally agreed configuration

Bleeding controlled?

YES
- Notify transfusion laboratory to: ‘Cease MTP’

NO

OPTIMISE:
- oxygenation
- cardiac output
- tissue perfusion
- metabolic state

MONITOR (every 30–60 mins):
- full blood count
- coagulation screen
- ionised calcium
- arterial blood gases

AIM FOR:
- temperature > 35°C
- pH > 7.2
- base excess < –6
- lactate < 4 mmol/L
- Ca²⁺ > 1.1 mmol/L
- platelets > 50 × 10⁹/L
- PT/APTT < 1.5 × normal
- INR ≤ 1.5
- fibrinogen > 1.0 g/L

The routine use of rFVIIa in trauma patients is not recommended due to its lack of effect on mortality (Grade B) and variable effect on morbidity (Grade C). Institutions may choose to develop a process for the use of rFVIIa where there is:

1. uncontrolled haemorrhage in salvageable patient, and
2. failed surgical or radiological measures to control bleeding, and
3. adequate blood component replacement, and
4. pH > 7.2, temperature > 34°C.

Discuss dose with haematologist/transfusion specialist. rFVIIa is not licensed for use in this situation; all use must be part of practice review.

### Specific surgical considerations

- If significant physiological derangement, consider damage control surgery or angiography.

### Cell salvage

- Consider use of cell salvage where appropriate.

### Resuscitation

- Avoid hypothermia, institute active warming.
- Avoid excessive crystalloid.
- Tolerate permissive hypotension (BP 80–100 mmHg systolic) until active bleeding controlled.
- Do not use haemoglobin alone as a transfusion trigger.

### Special clinical situations

- **Warfarin:**
  - add vitamin K, prothrombinex/FFP

- **Obstetric haemorrhage:**
  - early DIC often present; consider cryoprecipitate

- **Head injury:**
  - aim for platelet count > 100 \( \times 10^9/L \)
  - permissive hypotension contraindicated

- **Avoid hypothermia, institute active warming**
- **Avoid excessive crystalloid**
- **Tolerate permissive hypotension (BP 80–100 mmHg systolic)** until active bleeding controlled
- **Do not use haemoglobin alone as a transfusion trigger**

### Considerations for use of rFVIIa

- Actual or anticipated 4 units RBC in < 4 hrs, + haemodynamically unstable, +/- anticipated ongoing bleeding
- Severe thoracic, abdominal, pelvic or multiple long bone trauma
- Major obstetric, gastrointestinal or surgical bleeding

### Dosage

- **Platelet count < 50 \( \times 10^9/L \)**
  - 1 adult therapeutic dose
- **INR > 1.5**
  - FFP 15 mL/kg
- **Fibrinogen < 1.0 g/L**
  - cryoprecipitate 3–4 g
- **Tranexamic acid**
  - loading dose 1 g over 10 min, then infusion of 1 g over 8 hrs

\(^a\) Local transfusion laboratory to advise on number of units needed to provide this dose

### Initial management of bleeding

- Identify cause
- Initial measures:
  - compression
  - tourniquet
  - packing
- Surgical assessment:
  - early surgery or angiography to stop bleeding

**Suggested criteria for activation of MTP**

- **ABG**
- **INR**
- **DIC**
- **RBC**
- **FFP**
- **BP**
- **PT**
- **rFVIIa**
- **APTT**
- **MTP**
- **FBC**

**Acronyms and Abbreviations**

- **ABG** arterial blood gas
- **INR** international normalised ratio
- **DIC** disseminated intravascular coagulation
- **RBC** red blood cell
- **FFP** fresh frozen plasma
- **BP** blood pressure
- **PT** prothrombin time
- **rFVIIa** activated recombinant factor VII
- **APTT** activated partial thromboplastin time
- **MTP** massive transfusion protocol
- **FBC** full blood count
CRASH 2²

In trauma patients with, or at risk of, significant haemorrhage, tranexamic acid (loading dose 1 g over 10 minutes, followed by infusion of 1 g over 8 hours) should be considered.

The CRASH 2 trial² was published on 14 June 2010 after the cut-off date of the systematic review. No systematic review was conducted on tranexamic acid in critical bleeding/massive transfusion. The study population was not restricted to critical bleeding requiring massive transfusion.
CRASH-2 Study Limitations

- Only 1.4% of patients were in countries with consistent practices in trauma resuscitations and transfusion support
- Only 50.8% of patients were transfused
- Less than 50% of patients met BP or HR criteria
- Lack of clarity in patient care and monitoring
- Lack of ISS, EBL, serious adverse events

“…Potential adverse effects of TXA have also been reported....We believe that important knowledge gaps exist and that a targeted, prioritized research effort will contribute to the refinement of practice guidelines over time.”
<table>
<thead>
<tr>
<th>Priority 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
</tr>
<tr>
<td>Further information specifically on the potential negative effects that were identified in CRASH-2 and MATTERS. First, the increased risk of death from bleeding in the group that received initial TXA treatment 3 h or more after injury in CRASH-2 (6, 12). Second are the increased thrombotic events observed in MATTERS (7). There were significant increases in both deep vein thrombosis and pulmonary thromboembolism with the use of TXA in that study.</td>
</tr>
<tr>
<td>Further investigation of thromboembolic risk, especially in the context of damage-control resuscitation.</td>
</tr>
<tr>
<td>Potential complications and contraindicated subpopulations of trauma patients, including patients with TBI and potential impact of TXA on postoperative seizures.</td>
</tr>
<tr>
<td>Evaluation of patients who die after TXA – detailed examination for microthrombi, etc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Animal models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal models need to be developed/identified to support the efficacy, safety, and mechanistic studies of TXA.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional proof of efficacy and definition of what patients may benefit from TXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Properly designed trials to establish efficacy in patients treated to modern civilian and military trauma standards.</td>
</tr>
<tr>
<td>Better definition of which patients will benefit from TXA (e.g., penetrating wounds to the torso without shock; penetrating wounds to the torso with shock; polytrauma without shock; polytrauma with shock; isolated closed-head trauma; closed-head trauma with polytrauma).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information on the mechanism of action in traumatic hemorrhage. Multiple mechanisms have been proposed but not proven.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy and safety in isolated parenchymal brain injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information is needed on potential efficacy and safety in isolated parenchymal injury/bleeding of the brain.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prehospital use (in tactical combat casualty care)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential for use in the prehospital setting, with delayed evacuation, limited other supporting products (maybe no blood products or only plasma), and very early administration/alternative dose and timing.</td>
</tr>
<tr>
<td>Interactions with other prehospital resuscitation fluids and agents, impact of storage in the field environment.</td>
</tr>
<tr>
<td>Compatibility with the remote damage-control resuscitation concepts.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority 2</th>
<th>Efficacy and safety of TXA with administration beginning at various times after trauma.</th>
<th>What should be the “cutoff” time for TXA (what is the optimal window for administration)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal changes/optimal treatment window</td>
<td>Is the effect one of TXA, or TXA in combination with blood products, etc.?</td>
<td></td>
</tr>
<tr>
<td>TXA in combination with blood products</td>
<td>Potential routes of administration: intravenous, oral, IO”, transmucosal.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactions with inflammatory and coagulation systems</td>
</tr>
<tr>
<td>Dosing</td>
</tr>
<tr>
<td>Use with standard resuscitation fluids</td>
</tr>
<tr>
<td>Microcirculation</td>
</tr>
<tr>
<td>Drug interactions</td>
</tr>
</tbody>
</table>
“We have the evidence—we must use it in the service of humanity. It can take more than a decade for the results of medical research to become standard practice. This is too long.”

Shakur H et al. A promise to save 100,000 trauma patients. Lancet 2010; 380:2062
Hyperfibrinolysis was identified in the most severely injured patients, and correlated with mortality. [xxix], xxviii Kashuk et. al. demonstrated primary fibrinolysis in 34% of patients requiring massive transfusion using TEG. [xxx] Early administration of an anti-fibrinolytic agent (tranexamic acid) to adult trauma patients resulted in reduced all-cause mortality in the treatment group, reduced mortality from bleeding and a safe side effect profile in bleeding trauma patients. [xxxii] It is recognized, however, that severely injured patients who present fibrinolysis have increased mortality, xi, [xxxii] so the efficacy of tranexamic acid in such patients is questionable. TEG/ROTEM assays may signal the selection of patients who would most benefit from this intervention.
Take home message

- The clinical utility of tranexamic acid within a massive transfusion protocol remains a question mark that will need rigorous randomized control trials for answers.