Massive transfusion protocols is the expense justified?

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Blood Use - USA

- 13 million units collected, <5% outdated
- 10-12 million units transfused
- 4 million recipients
- 2/3 for surgery
- One-third emergency
- Type O blood - 200,000 units
- 35 transfusion-related deaths from blood incompatibility or infection
Complications of transfusion

- TRALI 8%
- Purpura 6%
- Disease 3%
- GVHD 2%
- Delayed Reaction 14%
- Acute Reaction 15%
- Blood Delivery Error 52%

52% (191/366) “wrong blood to patient”

only 1/14,000 units in USA
Reduction in transfusion

- Abdominal infection post injury. Only injury severity and number of units transfused and not the presence of colonic injury determined outcome.
  
  Kirton, J Trauma 2000.

- Transfusions increase incidence of Ventilator Acquired Pneumonia (VAP). Administration of 1-2 units doubles the VAP rate
  

- Transfusion trigger should be a haemoglobin of 70
  
  Hebert NEJM
Impact of transfusion on complications following trauma

Relationship between units of transfused blood in the first 12h and the incidence of MOF

Association between 0-15 units of pRBCs and infection rate

Blood transfusion requirement has a greater predictability of mortality than ISS

ISS and mortality as a function of the number of RBCs given. The increase in mortality with greater transfusion was highly significant (p=10^{-6}). ISS was significant only for the 1-10 units group (p=10^{-13})

Como JJ et al. Transfusion 2004; 44: 809-813
Deployment of Blood
Logistically Costly, Most Discarded

US Armed Forces Blood Program

Vietnam War
- Units deployed: 1,300,000
- Units discarded: 780,000

Gulf War
- Units deployed: 120,000
- Units discarded: 114,000

Benefits of transfusion

- Red cell transfusions are used to increase oxygen carrying capacity
- Augment $O_2$ delivery

Oxygen delivery = Cardiac output x Oxygen content

Many contemporary transfusion practices have no evidence base
Blood: Problems and risks

- Requires donors and cross-matching
- Limited shelf life (up to 42 days)
- Dysfunctional oxygen delivery
- Complications
  - Incompatibility reactions
  - Transmits infection
  - Immunomodulation
  - Metabolic consequences
Transfusion incompatibility

- Major incompatibility
  - ABO and previously sensitized
  - Cold autoantibodies
  - Intravascular haemolysis
  - Significant morbidity and mortality

Hospital staff error in 75% of cases
I confess that in 1901 I said to my brother Orville that man would not fly for 50 years.....

Ever since, I have distrusted myself and avoided all predictions

Wilbur Wright 1903
Transmission of infection

- Donor disease transmission
  - Hepatitis
  - HIV
  - Herpes, CMV and EBV
  - CJD
  - Malaria, Spirochetes

23 organisms known to be transmissible by blood transfusion
Immunomodulation

- Disrupts recipient immune function
- Down-regulates cellular immune response
- Critically ill patients
- Colonic cancer: Transfusion worsens prognosis
Microaggregates: Buffy coat

- ARDS
- Reticulo Endothelial System (RES) blockade
- Antigenic stimulation
- Stimulates acute phase response
- Clogging of microcirculation
Metabolic abnormalities

- Electrolytes and glucose
- Hypocalcaemia
- Acidosis
- Hypothermia
- Coagulopathy
  - Hypothermia
  - Dilution
  - Consumption of clotting factors
Disseminated intravascular coagulopathy (DIC)

Initiation of coagulation

Release of pro and anti-coagulants:
- Thrombin
- Plasmin
- Ongoing bleeding
- Endothelial dysfunction
- Microvascular coagulation
Management of red cell transfusion

- Hb and Haematocrit may be unreliable
- Look for clinical evidence of hypoxia
- Aim for Hb 80 – 100 g/L following haemorrhage control
- Use warmed PRBC only
Blood transfusion is like marriage...

It should not be entered upon lightly, unadvisedly or wantonly...

or more often than is absolutely necessary.”

R.W. Beal 1976
History of transfusion

1628 William Harvey
human circulation

1656 Christopher Wren
infused fluids (ale, wine, drugs) into dogs
1667: First animal transfusion

Denis (Paris) and Lower (London)
1799

George Washington:
...dead of sore throat

Doctors removed
2365cc Blood/12h
Traditional transfusion strategy

Alternatives

Current transfusion standards

Worsening haematological status

- Crystalloid or colloids
- Packed cells
- Fresh frozen plasma and/or cryoprecipitate
- Platelets
- Alternatives*

Blood volumes replaced

* PCCs, fresh whole blood, rFVIIa
So load your patient wisely!
Autologous blood transfusion

- Accepted for thoracic injuries
- Controversial if abdominal source
- Filtered “re-hung”
- MAXIMUM 1500 ml before DIC
- Cell salvage preferred
Intraoperative blood salvage

- Cell Saver
- No cross match
- No disease the patient hasn’t already got
- No transfusion reaction
- BUT
- Depletion of clotting factors
- Can precipitate DIC
- Hollow viscus injury issue
Platelets

- First abnormality to develop in the trauma patient is thrombocytopenia
- Platelets ineffective during acidosis, hypothermia, renal failure
Clotting factors

- Clinical versus laboratory diagnosis
- Consider prophylaxis after 2nd unit of blood
- Consider monitoring with thromboelastogram (TEG)

Fresh Frozen Plasma (FFP)
- Clotting factors same as whole blood
- Cryoprecipitate / Fibrinogen
- Smaller volume for same amount of factor
- Higher fibrinogen level
Massive transfusion: Definition

- Blood transfusion > 10 units
- Exchange of circulating blood volume in 24 hours
- 50% of predicted blood volume lost in three hours
- Based on 70 mL / Kg
Haemorrhage is responsible for 30-40% of trauma mortality

- Pre-hospital
- Coagulopathy
Coagulopathy that occurs after all surgical bleeding has been controlled:

- Dilution
- Consumption of clotting factors
- Hypothermia
Epidemiology of trauma

Trauma is a disease of the young

Most trauma deaths occur in young males

n=453,806 (US data from 1997–2002)

n=27,052 (US data from 1997–2002)

Reproduced with permission.
American College of Surgeons. National Trauma Data Bank™ Report 2003
- To improve oxygen delivery
- Myocardial ischaemia develops at an Hb of < 50 g/L
- Best measured with serum lactate
Cumulative Risks of Early Fresh Frozen Plasma, Cryoprecipitate and Platelet Transfusion in Europe

- Non haemolytic transfusion reactions
- Congestive cardiac failure
- Sepsis
- TRALI
- Post transfusion purpura
- Viral transmission
- Anaphylaxix
- Citrate toxicity
- Allo-immunisation
The Clinical Benefits of the Leukoreduction of Blood Products

M. A. Blajchman, MD, FRCP(C)

Many adverse events associated with the transfusion of allogeneic blood products have been shown to be related to the presence of allogeneic leukocytes in the blood product transfused. Until recently little attention has been paid to the leukocytes present in various blood components, however, over the past two decades it has been shown that the removal of such “passenger” leukocytes is associated with improved clinical outcomes. These include: the reduction in the incidence and severity of febrile transfusion reactions; reducing the CMV transfusion transmission risk; reducing the risk of alloimmune platelet refractoriness; the possible avoidance of vCJD transmission; as well as reducing the risk of mortality and organ dysfunction in cardiac surgery patients, and possibly in other categories of patients.

Key Words: Blood transfusion, Adverse events, Transfusion-related immunomodulation, TRIM, Transfusion-associated infections, Transfusion-associated mortality, Organ dysfunction, Blood products.

J Trauma. 2006;60:S83–S90.

- Reduction in incidence and severity of febrile reactions
- Reducing CMV transmission risk
- Reducing alloimmune platelet refractoriness
- Avoidance of vCJD transmission
- Reduction in MODS
Blood components

- Packed red cells
- Plasma
- Clotting factors
- Platelets

The United States has discovered this mix is called "Whole Blood"
The Use of Fresh Whole Blood in Massive Transfusion

Thomas B. Repine, MD, Jeremy G. Perkins, MD, David S. Kauvar, MD, and Lorne Blackborne, MD

Background: Most indications for whole blood transfusion are now well managed exclusively with blood component therapy, yet the use of fresh whole blood for resuscitating combat casualties has persisted in the U.S. military.

Methods: Published descriptions of whole blood use in military and civilian settings were compared with use of whole blood at the 31st Combat Support Hospital (31st CSH) stationed in Baghdad in 2004–2005.

Findings: Concerns about logistics, safety, and relative efficacy of whole blood versus component therapy have argued against the use of whole blood in most settings. However, military physicians have observed some distinct advantages in fresh warm whole blood over component therapy during the massive resuscitation of acidic, hypothermic, and coagulopathic trauma patients. In this critical role, fresh whole blood was eventually incorporated as an adjunct into a novel whole-blood-based massive transfusion protocol.

Conclusions: Under extreme and austere circumstances, the risk:benefit ratio of whole blood transfusion favors its use. Fresh whole blood may, at times, be advantageous even when conventional component therapy is available.

Key Words: Fresh whole blood, Massive transfusion, Trauma, Combat casualty care, Blood banking, Walking blood bank.
- Plasma coagulation concentrations rapidly drop to <40% of normal in trauma
- This occurs before 10 U have been transfused
- Associated with a precipitate drop in platelets to < 50 000
Transfusion guidelines

- Use packed red cells (PRBC)
- Use leucodepleted blood if massive transfusion expected
- Use cross-matched blood if available
Emergency blood
Baseline bloods

- FBC and Platelets
- PT, aPTT, INR
- Fibrinogen
- D-dimer

- Repeat after every 6 Units
Blood bank to issue...

- 6 Units PRBC
- 6 Units FFP
- 1 Apheresis Platelet Unit / 6 Units platelets
Mortality dynamics have changed

More efficacious EMS has shifted pre-hospital to early hospital death

Today most deaths occur within 12 hours upon arrival at hospital

Change of Mortality distribution over time

Late death due to post surgical complications is declining

Administration

- Micro-aggregate filters not advised
- 1:1 Blood:FFP
- 1 Unit of platelets per 6 Units
- Then repeat bloods
Additional...

- 4 Units FFP if PT or aPTT > 1.5 N
- 10 Units cryo if Fibrinogen < 1 gm / mL
- 10% CaCl if above are required
- Give additional unit of platelets if count <70 000 in presence of ongoing bleeding
Blood conservation

- Return all unused packs to blood bank within 6 hours
Endpoints

- No active bleeding
- No further need for red cells
- Temperature > 35° C
- Ph > 7.3
- Fibrinogen < 1.5 gm / L
- Clotting better than 1.5 normal
- Hb 80-100 gm / L
Massive transfusion protocol

- Return physiology to normal
  - Temperature
  - pH (Acidosis)
  - Check laboratory values
- After two units of transfused blood...
  - For every subsequent unit of blood transfused
    - FFP: 1 Unit (± 2 ml/Kg)
    - Platelets: 1 unit (or 1 apheresis Mega unit / 10 Units)
    - Cryoprecipitate / fibrinogen: 1 unit (non-responders)

If expected, initiate massive transfusion protocol
Adjuncts to bleeding control

- **Topical**
  - Interventional radiology
  - Zeolite mineral powder
  - Chitosan
  - Dry fibrin sealant dressings (DFSD)

- **Systemic**
  - Aprotinin
  - Desmopressin
  - Tranexamic acid
  - rFVII
Recombinant factor VIIa

- Not a drug of last resort
  - Less effective if pH < 7.2
  - If other clotting factors left
  - If platelet count low
- Should probably be given after administration of ± 6 units
What is rFVIIa?

- Structure
- Mechanism of action
- Potential uses
  - Coagulopathic patients
  - Severe trauma
rFVIIa Optimizes Localized Hemostasis

1. rFVIIa works at the site of vascular injury, where TF is expressed and activated platelets are found
2. In pharmacological doses, rFVIIa binds directly to the surface of activated platelets
3. rFVIIa enhances localized thrombin generation and fibrin clot formation, producing a stable clot

Picture modified with permission

Commonest mortality is from bleeding
rFVIIa successfully corrected acquired coagulopathy

- Case series of 81 patients with acute coagulopathy unresponsive to component therapy:
  - 46 cases of acute traumatic haemorrhage
- Prothrombin time visibly decreased in 78/78 cases after rFVIIa dose
- 61/81 patients were classed as responders to rFVIIa.
  - 34/61 responders survived to discharge
- No evidence of thrombus formation remote from the site of bleeding

Effect of a single median rFVIIa dose of 100 µg/kg (80–144 µg/kg)

Trial Background

- rFVIIa approved for patients with haemophilia and inhibitors
- Many anecdotal reports of its use in trauma. Therefore real need for a controlled trial
- Trauma trials are significantly complex
- Few placebo controlled trials
- Regulatory issues resulted in non-US study
- 32 centers in 8 countries
Trial Objective and Design

Objective:
- To evaluate the safety and efficacy of rFVIIa given as an adjunct to standard therapy in the treatment of hemorrhage in trauma patients

Design:
- Prospective, multi-center, randomized, double-blind, parallel-group, placebo-controlled
- Patients were randomized to one of two protocols based on whether the trauma was blunt or penetrating

Safety:
- Data Safety Monitoring Board
Entry Criteria

- **Inclusion criteria**
  - Injury due to blunt and/or penetrating trauma
  - Received 6 units of RBC within 4 hours of admission
  - Received 8 units of RBC prior to dosing

- **Exclusion criteria**
  - GCS < 8 or gunshot wound to the head
  - Severe acidosis pH < 7.0 or a base deficit > 15 mEq/L
  - Injury sustained > 12 h before randomization
Trial Design: Two studies – one protocol

Injury

- Arrival ER
- Randomization
  - RBC
    - 0
    - 6
    - 8

Time (hrs)
- 0 - 4
- 0 - 12

Treatment
- 200, 100, 100 μg/kg

- Transfusion requirements & Volume replacement
- ICU, hospital days
- Survival
- Adverse Events
- Serious Adverse events: MOF, ARDS, infections

rFVIIa

Placebo

48 hrs 30 days
Rationale for dose

Clearance in trauma patients is dependant on bleeding giving rise to a substantial variation in peak concentrations of rFVIIa
Primary endpoint

- Total number of units of RBCs transfused in the first 48 hours after the initial dose of trial product

  Transfusion was used as an endpoint for assessment of hemostatic effect
Secondary endpoints

- Hospitalization
  - Time on Ventilator
  - Time in ICU
  - Time in hospital

- Adverse events
  - (including thromboembolic events)

- Predefined complications (ARDS, MOF)

- 30-day survival
# Baseline Characteristics (277 patients)

<table>
<thead>
<tr>
<th>Mean (± SD)</th>
<th>BLUNT</th>
<th>PENETRATING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=74</td>
<td>rFVIIa n=69</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35 (13)</td>
<td>33 (13)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>52 (70%)</td>
<td>48 (70%)</td>
</tr>
<tr>
<td>ISS score</td>
<td>32 (13)</td>
<td>33 (13)</td>
</tr>
</tbody>
</table>
### Total RBC Transfusions (Units) During 48 Hours After First Dose of Trial Drug

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>rFVIIa</th>
<th>Est. RBC reduction*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (range)</td>
<td>n</td>
<td>Median (range)</td>
</tr>
<tr>
<td><strong>Blunt</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients†</td>
<td>72</td>
<td>7.2 (0–35)</td>
<td>64</td>
<td>7.8 (0–48)</td>
</tr>
<tr>
<td>Excluding 48h mortality</td>
<td>59</td>
<td>7.5 (0–35)</td>
<td>52</td>
<td>7.0 (0–29)</td>
</tr>
</tbody>
</table>
Bleeding is a major cause of death in trauma. Many trauma patients require blood transfusions.

- MOF: 7%
- Other: 4%
- Unknown: 2%
- CNS: 42%
- Bleeding: 39%
- Bleeding + CNS: 6%

N=289
Patients dying in hospital within 48 hours

6-15% are in shock

- One or more transfusions: 45%
- Massive transfusions (>20 U RBCs): 2%

References:
2. Annual Report German Trauma Register 2002
## Total RBC Transfusions (Units) During 48 Hours After First Dose of Trial Drug

<table>
<thead>
<tr>
<th>Penetrating</th>
<th>Placebo</th>
<th>rFVIIa</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
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<tr>
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</tr>
<tr>
<td>Excluding 48h mortality</td>
<td>52</td>
<td>4.2 (0–41)</td>
</tr>
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</table>
>20 unit* Transfusion requirement in the first 48 Hours

* >12 units after trial drug initiation in addition to >8 units before trial drug initiation. Patients alive at 48 hours.
FFP, platelet and cryoprecipitate requirements within 48 hours

*Patients surviving >48 hours
†p-value for the two-sided Wilcoxon-Mann-Whitney test
Incidence of adverse and thromboembolic events

Blunt trauma

- Placebo: n=59
- rFVIIa: n=53

Proportion of patients (%)

Penetrating trauma

- Placebo: n=43
- rFVIIa: n=46

Proportion of patients (%)

Adverse events

- Placebo: n=3
- rFVIIa: n=2

Thromboembolic events

- Placebo: n=3
- rFVIIa: n=4
## Secondary Endpoints at Day 30

<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
<th>Blunt trauma</th>
<th>Penetrating trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo (N = 74)</td>
<td>rFVIIa (N = 69)</td>
</tr>
<tr>
<td>ICU-free days *</td>
<td></td>
<td>8 (0-29)</td>
<td>13 (0-30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 (0-30)</td>
<td>23 (0-30)</td>
</tr>
<tr>
<td>Ventilator-free days *</td>
<td></td>
<td>14 (0-30)</td>
<td>17 (0-30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 (0-30)</td>
<td>26 (0-30)</td>
</tr>
</tbody>
</table>

*No statistical significance was observed for any of the groups*
Incidence of MOF, ARDS, and death through 30 days

Blunt Trauma

- MOF: Placebo n=9, rFVIIa n=5
- ARDS: Placebo n=12, rFVIIa n=3
- Death: Placebo n=17, rFVIIa n=22

Penetrating Trauma

- MOF: Placebo n=18, rFVIIa n=17
- ARDS: Placebo n=5, rFVIIa n=2
- Death: Placebo n=4, rFVIIa n=5

Predefined critical endpoints: multiple organ failure (MOF), acute respiratory distress syndrome (ARDS) and death
Reports of ARDS and MOF within 30 days
- Blunt trauma†

![Bar chart showing incidence of ARDS, MOF, and MOF or ARDS events with p-values for comparisons between Placebo and rFVIIa.](chart_image)

† Patients alive at 48 hours
*p-value for two-sided Fisher’s exact test
Conclusion

Patient Safety

- No safety issues were identified
- No increase in the incidence of thromboembolic events
- No increase of MOF or ARDS in either trauma group with rFVIIa vs placebo

Trends:
- More ventilator-free days
- More ICU-free days
Risks to benefit

- rFVIIa is an effective adjunctive treatment for blunt or penetrating trauma patients in situations where major bleeding has been controlled by surgical or other interventions.
- There is no significant effect on hospital mortality rate.
- A significant response is seen in blunt trauma and similar effects can be expected in penetrating trauma in cases of extensive tissue destruction, e.g. following high-velocity gunshot or close-range shotgun wounds.
- The benefits of increased bleeding control – reduced RBC transfusion need for massive transfusion translated into a lower risk of developing single or multiple organ failure, especially ARDS.
Risk to benefit

- For optimal effect, first dose of rFVIIa should be given at or immediately after initial surgical attempt to control the major bleeding sites.

- Patients who are unlikely to benefit from the drug:
  - Patients at low risk of residual or recurrent bleeding and who are not coagulopathic.
  - Patients in whom extensive bleeding cannot be surgically controlled, and whose state of physiological derangement is extremely advanced at time of surgical intervention.
Haemorrhage control

Controlling the bleeding and maintaining blood volume are the primary concerns in trauma management.

The treatment of bleeding is to stop the bleeding.
We don’t know...

- What is the correct dose?
- What is the correct dose interval?
- What are the correct indications?
- What is the correct cost of the drug?
- What is the reduced burden on society?
So....is the expense justified
We do know...

- Use may not yet be justified
  - Too early
  - Too expensive
  - Best benefits have yet to be proven

But properly used will be a major adjunct in the care of the bleeding patient.
Summary

- Blood and clotting factors are life saving
- Associated with serious complications
- Rational use is a clinical decision
- Develop a massive transfusion protocol
Thank you
Haemorrhage

- Circulating blood volume is maintained by
  - Replacing lost blood using volume expanders and red blood cells
  - Preventing further blood loss through surgery AND an effective coagulation process

- However
  - Transfusion increases the risk of complications following trauma
  - Coagulation process may be compromised (coagulopathy)