Massive transfusion: Recent advances, guidelines & strategies

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Massive Hemorrhage
Introduction

• Hemorrhage is a major cause of potentially preventable death
• Traumatic injury is the leading cause of death due to early hemorrhage within the first 6 hours after incurring injury
• These patients have a mortality ranging from 40 – 70%
• 25% of trauma patients receive a blood transfusion, with 3-5% of civilian traumas and 10% of military trauma patients receiving a massive transfusion (MT)
• Obstetric hemorrhage is the most common cause of shock in obstetric patients and is the leading cause of maternal mortality worldwide
• High mortality rate is due to ongoing hemorrhagic shock as a result of ‘lethal triad’ of coagulopathy, acidosis and hypothermia
History of transfusion

Major changes in blood transfusion practice occurred based on experience of military physicians during major wars

- **First world war (1917):** First use of preserved blood (O Neg) for transfusion in combination with saline and colloids
- **Second world war:** Albumin and lyophilised (freeze-dried) plasma were used in combination with whole blood to achieve balanced resuscitation
- **Vietnam war (1970s):** Practice changed from whole blood to component therapy – confusion as to how to use component therapy for MT
- **1980s:** Significant amount of crystalloids upfront on admission and blood components were considered much later after lab results. Failure to control bleeding led to vicious cycle of ‘lethal triad’
- **1990s:** Realised deleterious effects of crystalloids – return to the balanced resuscitation as that described in second world war
Massive hemorrhage

• **Massive hemorrhage is**
  – Loss of more than one blood volume within 24 hours
  – 50% of total blood volume lost in <3 hours
  – Bleeding in excess of 150 ml/min

**Massive blood loss is encountered in**

– Polytrauma
– Obstetric hemorrhage
– Gastrointestinal bleed
– Major surgeries (eg. cardiac, hepatobiliary, liver transplantation)
– Vascular surgeries

**Massive hemorrhage requires massive transfusion to maintain adequate circulation and hemostasis**
Trauma-induced coagulopathy

- This is an important predictor of blood utilization and trauma-related mortality
- It is iatrogenic or secondary to coagulopathy
- It is caused by dilution and consumption of coagulation factors from crystalloids & RBCs, hypothermia and acidosis
- Hypoperfusion and ischemia associated with trauma, causes release of activated protein C, which leads to consumption of plasminogen activator inhibitor (PAI-1), inhibition of the clotting cascade, systemic anticoagulation and hyperfibrinolysis
Point-of-care hemostatic assay

- TEG/ROTEM accurately monitors hemostasis
- Provides information to guide blood component therapy in a timely manner
- It differentiates between low fibrinogen and reduced platelet function as the cause of impaired clot strength and identifies systemic hyperfibrinolysis
- Turnaround time for these assays is shorter compared with conventional assays
Massive transfusion - Definition

- Massive transfusion (MT) is transfusion of large volume of blood products over a short period of time to a patient who has severe or uncontrolled hemorrhage
  - Transfusion of >10 red blood cell (RBC) units, which approximate one total blood volume (TBV) of an average adult patient, within 24 hours
  - Transfusion of >4 RBC units in 1 hour with anticipation of continued need for blood product support
  - Replacement of >50% of the TBV by blood products within 3 hours

In pediatric patients, because of age and weight variability in determining TBV, MT is defined as
- Transfusion of >100% TBV within 24 hours
- Transfusion support to replace ongoing hemorrhage of >10% TBV/min
- Replacement of >50% TBV by blood products within 3 hours
Clinical management in MT

• Hospitals must have a massive transfusion protocol in place
• Team leader (senior doctor at the scene) declares a massive hemorrhage situation and coordinates the management
• Immediate control of obvious bleeding (pressure, tourniquet, hemostatic dressings)
• MTP must be triggered immediately when a massive hemorrhage situation is declared (SBP < 90 mm Hg)
• Patient is kept warm and all transfused fluids including blood components are given in a blood warmer
• Standard venous thromboprophylaxis should be commenced after hemostasis has been secured
Algorithm for the management of massive hemorrhage – BCSH guidelines

1. Recognise blood loss and trigger major blood loss protocol

2. Take baseline blood samples before transfusion for:
   - Full blood count, group and save, clotting screen including Platelet count, Fibrinogen
   - Near-patient haemostasis testing if available

3. If trauma and <3h from injury, give tranexamic acid 1 g bolus over 10 minutes followed by IV infusion of 1 g over 8h (consider tranexamic acid 1 g bolus in non-traumatic)

4. Team leader to coordinate management and nominate a member of team to liaise with transfusion laboratory
   - State patient unique identifier and location when requesting components
   - To limit use of Group 0 NEG until patient group known, use 0 NEG units in females and consider 0 POS in males
   - Use group-specific blood as soon as available
   - Request agreed ratio of blood components (e.g. 6 units RBS and 4 units FFP). Send porter to lab to collect urgently

If bleeding continues

Until lab results are available:
   - Give further FFP 1L (4 units) per 6 units red cells
   - Consider cryoprecipitate (2 pools)
   - Consider platelets (1 adult therapeutic dose (ATD))

If lab results are available:

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<thead>
<tr>
<th>IF</th>
<th>GIVE</th>
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<tbody>
<tr>
<td>Falling Hb</td>
<td>Red cells</td>
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<tr>
<td>PT ratio &gt;1.5</td>
<td>FFP 15–20 mL/kg</td>
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<td>Fibrinogen &lt;1.5 g/L</td>
<td>Cryoprecipitate (2 pools)</td>
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<tr>
<td>Platelets &lt;75×10^9/L</td>
<td>Platelets 1 ATD</td>
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Continue cycle of clinical and laboratory monitoring and administration of ‘goal-directed’ blood component therapy until bleeding stops
What is massive transfusion protocol?

• In the past, patients with massive bleed were initially given colloid/crystalloid fluids. Blood products were administered later guided by lab results. In spite of this, blood loss continued due to delay in laboratory turnaround time and dilutional coagulopathy.

• Resuscitation of patients with massive hemorrhage has advanced from reactive, supportive treatment with crystalloid and red blood cell therapy to use standardized massive transfusion protocols (MTPs).

• MTPs are designed to interrupt the lethal triad of acidosis, hypothermia and coagulopathy that develops with MT, thereby improving patient outcome.

• Damage control resuscitation involves transfusion of blood products preemptively using a balanced ratio of plasma and platelets to red blood cells.
A well-defined MT protocol is a valuable tool to delineate how blood products are ordered, prepared, and delivered; determine laboratory algorithms to use as transfusion guidelines.

To practice damage control resuscitation and to administer blood products early in the resuscitation.
Evidence-based recommendations are needed to guide the acute management of The bleeding trauma patients which when implemented may improve patient Outcomes.
Damage control resuscitation

• Severity of hemorrhagic shock is determined
• Rapid control of surgical bleeding
• Early and increased use of red blood cells, plasma and platelets in a ratio of 1:1:1
• Limitation of excessive crystalloid use
• Prevention and treatment of hypothermia, hypocalcemia and acidosis
• Hypotensive resuscitation strategies (SBP 80-100 mm Hg)
• Frequent lab tests (ABG, lactate, ionized Ca++, PT, APTT, platelet count, fibrinogen levels, apart from TEG)
MTP ratios

Protocol 1 - 6:4:1
- An MTP was established initially for trauma, labor & delivery and for surgical and critical care patients, which provides for emergency release of 6 U of PRBC, 4 U of plasma, and 1 apheresis platelet unit. This order set is issued within 6-10 minutes after oral telephone order. This combination achieves replacement of 70% of RBC volume and 60% of circulating plasma volume for a 70-kg individual

Protocol 2 – 1:1:1
- Recent military experiences, and better understanding the pathophysiology of trauma induced coagulopathy has led to early use of RBCs, plasma and platelets in a 1:1:1 ratio, this 645 ml product has a hematocrit of 29%, coagulation factor activity of 65%, and a platelet count of 90,000/µl. This closely resembles whole blood, which treats and prevents trauma-induced coagulopathy
- After the controlled ratio-driven intervention is completed, patients are treated with laboratory-guided blood component therapy
Resuscitation with a 1:1:1 ratio of RBCs, plasma and platelets is the recommendation of the Army surgeon General and his Trauma consultant.
Records of 466 MT trauma patients from 16 level 1 trauma centers between July 2005 and June 2006 were reviewed.

Survival in civilian MT patients is associated with increased plasma and platelet ratios. Massive transfusion practice guidelines should aim for a 1:1:1 ratio of plasma:platelets:RBCs.
PROMMTT study
Prospective observational multicenter major trauma transfusion study

- This study examined the association between mortality rates in trauma patients and transfusion ratios
- This cohort study demonstrated improved in-hospital mortality with RBC:plasma and RBC:platelet ratios <2:1 in the first 6 hours
PROPPR study
Pragmatic randomized optimal platelet and plasma ratios

• This is a randomized trial to evaluate ratios
• MT patients receive either a 1:1:1 (higher ratio) or a 2:1:1 (lower ratio) RBC:plasma:platelets with primary outcome of survival, complications and length of hospital stay
• No significant differences in overall mortality at 24 hours or 30 days were detected with two transfusion ratios studied
• More patients in 1:1:1 group achieved hemostasis and decreased hemorrhage related deaths over the first 24 hours
Red cell transfusion

- Red blood cells: Red cell transfusion is indicated when there is rapid blood loss >40%
- After major acute blood loss, blood transfusion is based on clinical picture and observations, as initial hematocrit/Hgb may be misleading
- Red cell units are transfused to restore oxygen-carrying capacity, based on clinical status, PvO2 and extraction ratio(ER)
- For immediate transfusion, group O red cells should be issued and for females in reproductive age group, Rh D negative red cells are issued
- ABO-group specific red cells can be issued once blood group is known, by type and screen/electronic cross match
- Use of intra-operative red cell salvage devices reduces the need for allogeneic blood, in appropriate cases
Autologous transfusion-Massive hemorrhage

- Use of intra-operative red cell salvage is effective in reducing demand on allogeneic blood and provides a readily available red cell supply in massive hemorrhage of
  - Obstetric hemorrhage
  - Intra-op massive hemorrhage during complex surgeries like liver transplantation
  - Major blood loss in patients with rare blood groups
Goal-directed blood component therapy

- Later in resuscitation, abnormal lab values such as prolonged PT and/or aPTT, low platelet count and low fibrinogen values are addressed individually.
- FFP is given in dose of 15 ml/kg if INR >1.5
- 1 SDP/6 RDPs are given if Platelet count <80-100,000/μL
- 10 u pooled cryoprecipitate is given if fibrinogen <125 mg/dL
- Blood products & crystalloids are given in rapid transfusion device and blood warmer
Type switches

O Negative red cells and AB FFP

- O- : O-, O+
- A- : A-, O-, A+, O+
- B- : B-, O-, B+, O+
- AB- : AB-, A-, B-, O-, AB+, A+, B+, O+
- O+ : O+, O-
- A+ : A+, O+, A-, O-
- B+ : B+, O+, B-, O-
- AB+ : AB+, A+, B+, O+, AB-, A-, B-, O-
Role of fresh whole blood in massive hemorrhage

• In combat setting, fresh whole blood has been used in situations where fractionated blood products are not available
• In a report of US military patients in Iraq and Afghanistan from January 2004 to October 2007, those with hemorrhagic shock, a resuscitation strategy that included fresh whole blood was associated with improved 30-day survival (95% vs 82%, p=0.002)
• In civilian trauma with the implementation of fractionated blood components, routine use of fresh whole blood for resuscitation of bleeding patients was abandoned
• In civilian trauma, blood components are given in a ratio of 1:1:1 (RBC:plasma:platelets), which is close to whole blood, with a better yield of individual components
Hemostatic agents

• **Recombinant activated factor VII (rFVIIa):** This is considered as a rescue therapy in patients with life-threatening bleeding that is unresponsive to standard hemostatic therapy. Recommended dose is 90 µg/kg.
  
  **CONTROL trial,** a phase 3 randomized clinical trial states that rFVIIa did not change mortality in patients with trauma. Rate of arterial thrombo-embolic events were higher among those who received rFVIIa.

• **Antifibrinolytics:** Hyperfibrinolysis contribute significantly to coagulopathy and antifibrinolytics agents reduce blood loss in patients with exaggerated fibrinolysis.
  
  **CRASH–2 trial:** In a placebo controlled randomized study, including 20,211 adult trauma patients, tranexamic acid as compared to placebo significantly decreased all-cause mortality from 16% - 14.5%, p=0.0035. Patients received either 1 g of tranexamic acid over 10 min followed by an IV infusion of 1 g over 8 hours or placebo. In 2011, the CRASH-2 investigators published that earlier treatment, within 3 hours from injury, is more effective in reducing the risk of death due to bleeding. However, patients receiving tranexamic acid >3 hours from injury had a significantly increased risk of death compared to placebo.
Hemostatic agents contd..

- **Fibrinogen concentrate**: Fibrinogen is the first hemostatic component that declines to pathologically low levels following trauma and/or hemodilution.
- Recent data indicate that coagulopathy induced by synthetic colloids such as HES may be reversed by administration of fibrinogen concentrate.
- Use of fibrinogen concentrate in patients with established hypofibrinogenemia, diagnosed by TEG/fibrinogen levels <100 mg/dl, in addition to balanced administration of RBC, FFP and platelets, contribute to faster achievement of a normal hemostasis in massively bleeding patients.
Hemostatic agents contd..

- **Prothrombin complex concentrate**: PCC contains coagulation factors II, VII, IX and X that are essential for thrombin generation. Carvalho et al. reported that administration of PCC to patients with massive bleeding had beneficial effect on hemostasis.

- **Factor XIII**: FXIII is important for clot firmness by binding to platelets through the GPIIb/IIIa receptor and by cross linking fibrin and increasing the resistance of the formed clot against fibrinolysis. Role of FXIII in bleeding trauma patients has to be investigated in randomized clinical trials.

- **Teragnostic approach**: A new approach to resuscitation of patients with massive blood loss was introduced using goal-directed administration of pharmacological agents such as fibrinogen concentrate, PCC, rFVIIa, and FXIII as alternatives to FFP, cryo and platelet concentrates together with volume resuscitation with synthetic colloids.
Arterial embolization

- Successful cessation of bleeding can be achieved with embolization of bleeding arteries following angiographic imaging
- This technique can be remarkably effective in controlling bleeding and may eliminate the need for surgical intervention particularly in major obstetric hemorrhage
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<th>Elective surgery</th>
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<tr>
<td>Tissue trauma</td>
<td>Controlled</td>
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<td>Initiation of</td>
<td>No delay between hemorrhage and initiation of</td>
<td>The interval between hemorrhage and</td>
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<td>massive transfusion</td>
<td>treatment</td>
<td>treatment can vary widely</td>
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<td>Volume status/shock</td>
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<td>Monitoring of</td>
<td>Ongoing. Anticipation of hemostatic defects is</td>
<td>Late. Laboratory tests are obtained when</td>
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<td>Coagulopathy</td>
<td>More often related to decreased coagulation factors</td>
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Massive transfusion associated with liver transplantation

• This group of patients are very sick and have underlying hemostatic abnormalities
• MTP ratio is 6:4:1 and 10 u of pooled cryo for every 10 u of red cell units
• If there is ongoing red cell salvage, simultaneous supplementation of allogeneic FFP, platelets and cryo is done
Obstetric hemorrhage

• Massive obstetric bleed is a major cause of maternal death and morbidity
• Degree of hemorrhage is out of proportion with the duration and the patient usually presents with shock
• MTP ratio is 6:4:1 (RBC:plasma:platelets) and ten units of pooled cryo is given for every 10 units of PRBC
• Early administration of Tranexamic acid prevents hyper fibrinolysis, which is common in obstetric hemorrhage
• rFVIIa is given in uncontrolled PPH
• Oxytocin and prostaglandin is given for uterine atony
• Appropriate surgical intervention
• Arterial embolization
Massive transfusion protocol provides early access to red blood cells, plasma, and Platelets(6:4:1) for patients experiencing severe postpartum hemorrhage. Favorable hematological indices were observed post resuscitation.
Summary

• Optimal management of massive transfusion requires coordination between clinical, laboratory and hematology teams
• Limitation of excessive crystalloid use
• Early resuscitation using evidence-based MT protocol appears to improve outcome
• Early administration of plasma and platelets along with red cells and earliest possible goal-directed blood component therapy based on results of TEG, reduces mortality and improves patient outcome
• Close monitoring of metabolic and coagulation function is essential to prevent the lethal triad of hypothermia, acidosis, and coagulopathy in massively bleeding patients
Thank you for your attention !!!