Massive Hemorrhage

Dr. Nevine Nabil Mostafa
Professor of clinical hematology,
Hemato-oncology and stem cell transplantation.
Ain Shams University, Cairo, Egypt

Death from injury has increased by 20% over the last decade and accounts for more deaths than malaria, tuberculosis, and HIV combined. **(1)**

Hemorrhage requiring massive transfusion secondary to trauma and major surgery remains a major cause of potentially preventable deaths, and development of coagulopathy further substantially increases the mortality rates of hemorrhaging patients **(2)**

Classically, massive transfusion has been defined as receiving 10 red blood cell (RBC) units in 24 hours, although recently, a change toward applying the rate of transfusion in a shorter time frame such as 2 or 6 hours has been broadly accepted. **(3)**

Massive blood loss is arbitrarily defined as the loss of one blood volume within a 24 h period **(4).** The normal adult blood volume being approximately 7% of ideal body weight in adults and 8–9% in children. Alternative definitions that may be more helpful in the acute situation include a 50% blood volume loss within 3 h or a rate of loss of 150 ml/min **(5)**

Class of haemorrhagic shock				
	I	II	III	IV
Blood loss (mL)	Up to 750	750–1500	1500–2000	> 2000
Blood loss (% blood volume)	Up to 15	15–30	30–40	> 40
Pulse rate (per minute)	< 100	100–120	120–140	> 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate (per minute)	14–20	20–30	30–40	> 35
Urine output (mL/hour)	> 30	20–30	5–15	Negligible
Central nervous system/ mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

It is imperative to recognize major blood loss early and institute effective action promptly if shock and its consequences are to be prevented.

Therapeutic goals are;
• Maintenance of tissue perfusion and oxygenation by restoration of blood volume and hemoglobin.
• Arrest of bleeding by treating any traumatic, surgical or obstetric source.
• Judicious use of blood component therapy to correct coagulopathy.

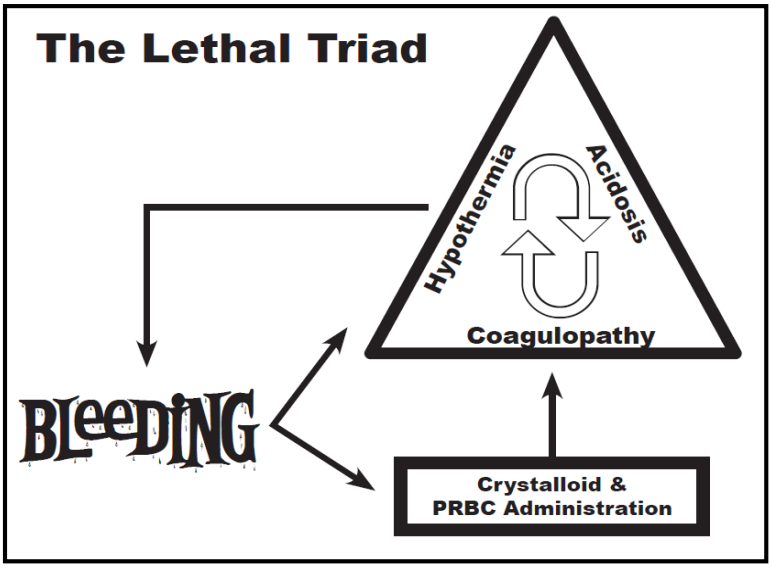
Restoration of circulating volume is initially achieved by rapid infusion of crystalloid or colloid through large bore (up to 14 gauge) peripheral cannulae **(6)**

Alternatively, larger bore central access devices can be used dependent on local skills and availability .The use of albumin and non-albumin colloids versus crystalloids for volume replacement has been the subject of debate following controversial meta-analyses **(7)**

A controlled trial of normal saline versus 4% human albumin for fluid resuscitation involving over 7000 patients in 16 intensive Care Units in Australia and New Zealand found no difference in outcome at 28 days and concluded that they were clinically equivalent (Grade A recommendation, Level 1b evidence). **(8)**

Hypothermia increases the risk of end organ failure and coagulopathy and may be prevented by pre-warming of resuscitation fluids, patient warming devices such as

warm air blankets and the use of temperature controlled blood warmers (Grade C recommendation, Level IV evidence). **(9)**



Key Parameters and Assessment of Trauma-Induced Coagulopathy

Beside the discussion about the substitution of coagulation factors and blood components, there is evolving knowledge that trauma itself has time- or incident-depending effects on coagulation **(10)**

Initially the combination of traumatic injury and tissue hypo-perfusion results in a coagulopathy associated with a reduction in protein C levels. Activated protein C exerts its anticoagulant effects by irreversibly inactivating factors Va and VIIIa **(11)**

A further anticoagulant activity is exerted by the de-activation of plasminogen activator inhibitor (PAI-1), resulting in enhanced fibrinolysis **(12)**

In addition to its anticoagulatory effects, protein C proteolytically activates the cell surface receptor protease-activated receptor-1 (PAR-1) and thus generates several cytoprotective effects by increasing the anti-inflammatory properties, anti-apoptotic activity, and protective function of the endothelial barrier, all being required for survival in acute shock **(13)**

Taken together, early post- traumatic coagulopathy is characterized by systemic anticoagulation/ coagulopathy in conjunction with hyperfibrinolysis **(14)**

Acidosis is often seen in massively transfused patients. There are two major components responsible for this pathologic state: anaerobic metabolism (lactate production) in hypoperfused tissues and excessive administration of chloride as NaCl or NaCl-based colloids. The infusion of these solutions should therefore be minimized **(15)**

Acidosis is responsible for impaired coagulation as the optimal range for the function of coagulation is left. Therefore, during the volume substitution of hemorrhage, acidosis or aggravation of acidosis in terms of dilutional coagulopathy or dilutional acidosis must be avoided. The best strategy to prevent acidosis is to avoid NaCl and to treat hemorrhage-associated acidosis is the use of plasma-equivalent electrolyte-based solutions.

Hypocalcemia is often linked with acidosis and aggravated by citrate. The content of free ionized Ca2+, which is necessary for the assembly of coagulation factors on the surfaces of platelets and injured endothelium, is inversely correlated with blood pH **(16)**

Calcium ions are essential not only for fibrin polymerization and platelet function but also for fibrinolysis and activation of the protein C system. Citrate- containing blood components, especially fresh frozen plasma (FFP), and in addition synthetic colloids promote the development of hypocalcemia **(17)**

Lactate, which usually increases during massive bleeding, causes a linear decrease in Ca2+ concentration. This phenomenon is estimated by an increase of 0.05 mmol/l Ca2+ per 1 mmol/l lactate. Thus, a concentration of 10 mmol/l lactate results in a reduction 0.5 mmol/l Ca2+ and thus usually in a relevant severe hypocalcemia requiring urgent therapy. The application of lactate-containing fluids like Ringer's lactate should therefore be diminished. All solutions should contain at least physiologic levels of calcium. **(18)**

(Johansson et al, 2014)

Massive Transfusion Protocol (MTP)

Appropriate Initial Interventions:

- **Intravenous access – 2 large bore IVs and CVC**
- **Crystalloid -3:1/colloid- 1:1 ratio with Expected blood loss**
- **Limited crystalloid - avoid dilutional coagulopathy**
- **Labs: Type & Crossmatch, CBC, Platelets, INR, PT, PTT, Fibrinogen, Electrolytes, BUN/Creatinine, ionized calcium**
- **Continuous monitoring: Volume Status, U/O, Acid-base status**
- **Aggressive re-warming.**
- **Prevent / Reverse acidosis**
- **Correct hypocalcemia: Calcium Gluconate or Calcium Chloride: 1 gm iv 10 slowly(Target goal ionized calcium 1.2 – 1.3)**
- **Transfuse with unmatched group O RBCs on hand.**
- **Repeat lab testing to evaluate coagulopathy**

Treatment of Trauma-Induced Coagulopathy

Fresh Frozen Plasma

Due to dilution, consumption, and inhibition of coagulation any major blood loss leads to a hypocoagulable state. There is growing evidence that early and more aggressive replacement of clotting factors reduces mortality and decreases transfusion volume **(19)**

Early standard use of FFP and pRBCs has been shown rather to prevent than to treat a severe dilutional coagulopathy and might contribute to an improved survival. It was estimated that 1–1.5 units of FFP must be given per unit of pRBC just to correct the dilutional component of coagulation alone. A higher FFP:pRBC ratio would lead to anemia, thrombocytopenia, and an increase of the volume overload. **(20)**

Fibrinogen

Massive bleeding leads to loss, consumption, and dilution (by volume therapy) of coagulation factors. The first factor falling below a critical level is fibrinogen. The critical threshold was suspected at a level below 100 mg/dl as shown by Hiippala et al. **(21)** and was still recommended as a trigger for intervention in a European Guideline in 2007 **(22)**

Under normovolemic conditions, a loss of the 1.4-fold of the patients' total blood volume and resuscitation with plasma-free solutions is associated with that critical level. One has to take into account that all colloids interfere with the measurement of fibrinogen **(23)**

FFP is not suitable for a rapid increase in already reduced fibrinogen plasma levels. We therefore recommend in patients with severe blood loss and ongoing bleeding to keep the fibrinogen level in a proactive fashion above 150 mg/dl to avoid additional decline by further dilution and consumption. Experience showed that a dose of 3g fibrinogen is practicable to ensure fibrinogen levels above the indicated threshold, although until now no prospective randomized trial is available which confirms such a dosage to be optimal.

Cryoprecipitate

Cryoprecipitate is a preparation rich in fibrinogen, factor XIII, von Willebrand factor, and factor VIII and has been used for therapy of fibrinogen or factor XIII deficiency **(24)**

In Europe, however, the use has been reduced due to the marketing authorization and permanent availability of single factor concentrates **(25)**

As FFP is not sufficient to raise plasma fibrinogen, in the USA and in the UK cryoprecipitate is accepted as alternative for the replacement of plasma fibrinogen **(26)**

Prothrombin Complex Concentrate

The prothrombin complex concentrate (PCC) contains vitamin K-dependent coagulation factors II, VII, IX and X, which are essential for the generation of thrombin and natural anticoagulants C and S. It is widely used for the therapy of inherited coagulation defects or the reversal of vitamin K antagonists **(27)**

In some studies with a small number of patients, the application of PCC was beneficial. However, there is no consensus about the use of PCC in the setting of severe bleeding and massive transfusion.

Recombinant Factor VIIa

Originally factor VIIa has been developed for patients with different types of hemophilia and inherited factor VIIa deficiency. For a long time, there have been enthusiastic opinions about the use of supraphysiologic doses of recombinant factor VIIa **(28)**

There was a significant increase of arterial thromboembolic events, in particular in patients where factor VIIa was used off label **(29)**

Therefore, the initial approach has still to focus on the correction of hemorrhagic shock, acidosis, and thrombocytopenia ensuring adequate hemostasis **(30)**

In patients with trauma-induced coagulopathies, persisting hemorrhage, and ineffective replacement of coagulation factors, the use of recombinant factor VIIa (initial dose of 100 µg/kg body weight) might be indicated as ultimate ratio, preferably after an accompanying severe acidosis is successfully treated.

Factor XIII

The function of factor XIII is the stabilization of the clot by forming covalent bonds between fibrin monomers and by cross-linking alpha-2 antiplasmin, fibrinogen, fibronectin, collagen, and other proteins to enhance the mechanical strength of the fibrin clot and protect the clot from proteolytic degradation **(31)**

Platelets

During acute blood loss, bone marrow and spleen release platelets into the circulation, and therefore their decrease in the peripheral blood is delayed in the acute clinical situation often the question comes up when thrombocytopenia has to be expected. After massive transfusion of pRBCs and FFP exclusively (e.g. >20 units), a severe thrombocytopenia occurs frequently.

The standard recommendation is to keep the platelet count at least above 50,000/µl in the acute scenario. Due to progress in noninvasive cardiovascular procedures, there is an increasing number of patients who were already receiving anticoagulatory therapy mainly targeting thrombocytes, e.g. acetyl salicic acid or glycoprotein IIb/IIIa inhibitors.

In these patients, platelet transfusions (e.g. 2 units initially) are strongly advised in case of active bleeding trauma, even at higher platelet counts **(32)**

However, a purely prophylactic administration or a continuation after stopping the bleeding should be avoided as this might increase the rate of thrombosis in this population of patients.

Antifibrinolytic drugs

Antifibrinolytic drugs, such as tranexamic acid and aprotinin, have been used to reverse established fibrinolysis in the setting of massive blood transfusion. **(33)**

Systematic reviews concluded that there is insufficient evidence from randomized controlled trials of antifibrinolytic agents in trauma to either support or refute a clinically important treatment effect and recent evidence is conflicting **(34)**

Conclusion

Fortunately, only a small percentage of trauma patients will require massive transfusion. However, in these patients there is a significant amount of primary trauma-induced coagulopathy which is aggravated secondarily by dilution and consumption of coagulation factors and platelets, requiring interdisciplinary teamwork in the emergency room without any delay.

The implementation of a well-structured worksheet and standard operating procedures with clearly allocated tasks and therapeutic options is necessary to improve the clinical outcomes of patients with life-threating massive hemorrhage.

These patients should benefit from the optimal management of fluid resuscitation, massive blood transfusion (early change to a fixed ratio of FFP:pRBCs of 1:1), and the treatment of trauma-induced coagulopathy (e.g. with tranexamic acid).

The use of recombinant factor VIIa is only justified if replacement therapy of blood components and coagulation factors fail in stopping major bleedings.

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