Introduction

Hemorrhagic shock accounts for 80% of deaths in the operating theatre and up to 50% of deaths in the first 24 hour after injury **(Westerman *et al.*, 2008)**.

Massive hemorrhage can be considered as a situation where 1-1.5 blood volumes may need to be infused either acutely or within a 24 hour period **(Rossaint *et al.*, 2010)**.

Hemorrhage in trauma is the combined result of blood loss and consumption coagulopathy, with potentiating effects of acidosis, hypothermia, and electrolyte disturbance. Moreover, severe tissue injury and hypoperfusion have been identified as important drivers of an endogenous trauma-related coagulopathy that is associated with poor outcome **(Frith *et al.*, 2010)**.

Massive blood transfusion is a conventional treatment, which is defined as the transfusion of at least 10 units of PRBCs within 24 hours **(Greer *et al.*, 2010).**

Coagulopathy, hypothermia, acidosis, electrolyte abnormalities, infections and immunomodulatory phenomena, which lead to multi-system organ dysfunction, all are complications of massive blood transfusion **(Lier *et al.*, 2008)**.

Due to these disadvantages and already low supplies of fresh blood, safe, available and effective alternatives substitute banked blood. Alternatives to correct coagulopathy such as fibrinogen, prothrombin complex and recombinant F VII and or attractive alternatives to allogenic red blood cells as perfluorocarbons (PFCs), have been recently considered **(Riess, 2005).**

Aim of the Essay

The aim of this essay is to focus on the treatment alternatives of massive hemorrhage to avoid obstacles and complications induced by conventional treatment.

Pathophysiology of massive hemorrhage

Massive hemorrhage can be considered as a situation where 1-1.5 blood volumes may need to be infused either acutely or within a 24 hour period **(Rossaint *et al*., 2010).**

Physiologic consideration in massive hemorrhage

The average adult blood volume represents 7% of body weight or 70 ml/kg of body weight **(Kasuya *et al*., 2003).**

Hemorrhage results in a fall in blood volume and therefore a fall in venous pressure and venous return to the heart **(Magder, 2006)**.

The consequent fall in preload to the atria causes a reduction in stroke volume of both right and left ventricles. The reduced arterial pulse pressure diminishes stretch on arterial baroreceptors, which results in an increased sympathetic output, causing vasoconstriction and reflex tachycardia which tends to

compensate for the reduced stroke volume, so cardiac output is initially preserved **(Marik *et al*., 2009)**.

As hemorrhage increases (but while shock is still reversible), bradycardia occurs. With continued hemorrhage, however, the tachycardia reappears. The vessels of the heart and brain are the only ones spared from vasoconstriction, which serves to preserve the blood flow to these two organs least able to recover from ischemia (**Santos *et al.*, 2009).**

Coronary vasodilation occurs because of the increased metabolic demands of the myocardium resulting from the tachycardia. The vasoconstriction is most marked in the skin, kidneys and viscera which explain some of the symptoms, signs and late sequelae of hemorrhagic shock. Widespread reflex venoconstriction also helps to maintain the filling pressure of the heart **(Laughlin *et al*., 2012)**.

Reduction in oxygen carrying capacity and flow cause anemic and stagnant hypoxia which combined with acidosis to stimulate chemoreceptors. This stimulates respiration and

excites the vasomotor centre, causing further vasoconstriction **(Dean, 2010)**.

Angiotensin II and renin increase aldosterone secretion which combined with renin cause salt and water retention to re-expand the blood volume. Constricted arterioles and reduced venous pressure combine to reduce the hydrostatic pressure in capillaries, which causes a net shift of fluid from the interstitial fluid to the capillaries, and in turn, from cells to the interstitium **(Friis *et al*., 2013).**

After moderate (1000 ml) blood loss in a normal subject, plasma volume is restored in 12–72 hours. Preformed albumin rapidly enters the circulation from extravascular stores, protein free fluid is mobilized from tissue fluids, which dilute plasma proteins and cells, but the reduction in hematocrit may take several hours **(Jacob *et al*., 2008)**.

The outcome of hemorrhagic shock depends largely on the volume of blood lost. Some patients will die soon after hemorrhage, while others recover as compensatory mechanisms (combined with treatment) restore the circulation to normal. An intermediate group of patients remain in a shocked state for several hours and gradually become unresponsive to

vasopressor drugs and even when blood volume is restored to normal, cardiac output remains depressed **(Backer *et al*., 2010).**

Refractory shock occurs when the compensatory response of vasoconstriction is prolonged and causes hypoxic tissue damage particularly in the splanchnic region. After about 4 hours, the pre capillary sphincters dilate so that blood can enter these capillaries but it stagnates because the venules remain constricted. Capillary hydrostatic pressure increases, causing net loss of fluid to the interstitium (**Waterhouse *et al.*, 2013).**

Cerebral ischemia depresses the vasomotor and cardiac areas of the brain, causing vasodilation and reduced heart rate.The blood pressure further decreases, which worsens the reduced cerebral blood flow and therefore further depresses the vasomotor and cardiac areas. Similarly, coronary blood flow is reduced because of hypotension and tachycardia despite coronary vasodilation. Myocardial depression worsens the shock and acidosis, which in turn worsen the myocardial failure. If the myocardium is sufficiently compromised, it reaches a point where it can no longer restore normal cardiac output even when the blood volume is restored to normal (**Maeder *et al*., 2013)**.

Classification system for acute blood loss

The American College of Surgeons has proposed the following classification system for acute blood loss **(Gutierrez *et al*., 2004).**

Table (1): Classification system for acute blood loss

	Class			
Parameter	**I**	**II**	**III**	**IV**
Blood loss (ml)	**< 750**	**750-1500**	**1500-2000**	**>2000**
Blood loss (%)	**<15**	**15-30**	**30-40**	**>40**
Heart rate (bpm)	**<100**	**>100**	**>120**	**>140**
Blood pressure	**Normal**	**Orthostatic**	**Hypotension**	**Severe hypotension**
CNS symptoms	**Normal**	**Anxious**	**Confused**	**Obtunded**

(Gutierrez *et al*., 2004)

Class I

Loss of ≤ 15% of the blood volume (or ≤ 10 ml/kg). This degree of blood loss is usually fully compensated by transcapillary refill. Because blood volume is maintained, clinical findings are minimal or absent and volume resuscitation is not necessary **(Gutierrez *et al*., 2004).**

Class II

Loss of 15–30% of the blood volume (or 10–20 ml/kg). This represents the compensated phase of hypovolemia, where blood pressure is maintained by systemic vasoconstriction **(Gutierrez *et al*., 2004).**

The vasoconstrictor response to hypovolemia is most intense in the splanchnic circulation, and splanchnic hypoperfusion can lead to disruption of the intestinal mucosa and invasion of the bloodstream with enteric pathogens **(Kolkman *et al*., 2008).**

Class III

Loss of 30–45% of the blood volume (or 20–30 ml/kg). This marks the onset of decompensated blood loss or hemorrhagic shock, where the vasoconstrictor response is no longer able to sustain blood pressure and organ perfusion. The clinical consequences can include supine hypotension, evidence of impaired organ perfusion (e.g., cool extremities, oliguria, depressed consciousness), and evidence of anerobic metabolism (i.e., lactate accumulation in blood) **(Gutierrez *et al*., 2004).**

Class IV

Loss of >45% of blood volume (or >30 mL/kg). This degree of blood loss results in profound hemorrhagic shock, which may be irreversible. Clinical manifestations include multiorgan failure and severe metabolic (lactic) acidosis **(Gutierrez *et al*., 2004).**

Loss of 30–40% of blood volume leads to hemorrhagic shock with a coagulopathy, whereas loss of more than 40% of blood volume is life threatening, with failure of perfusion of vital organs **(Garrioch, 2004).**

Coagulopathy in massive hemorrhage:

The coagulopathy is generally multifactorial with the main contributors being hemodilution, hypothermia, consumptive coagulopathy, acidosis and activation of the coagulation and fibrinolytic cascades **(Ganter and Pittet, 2010).**

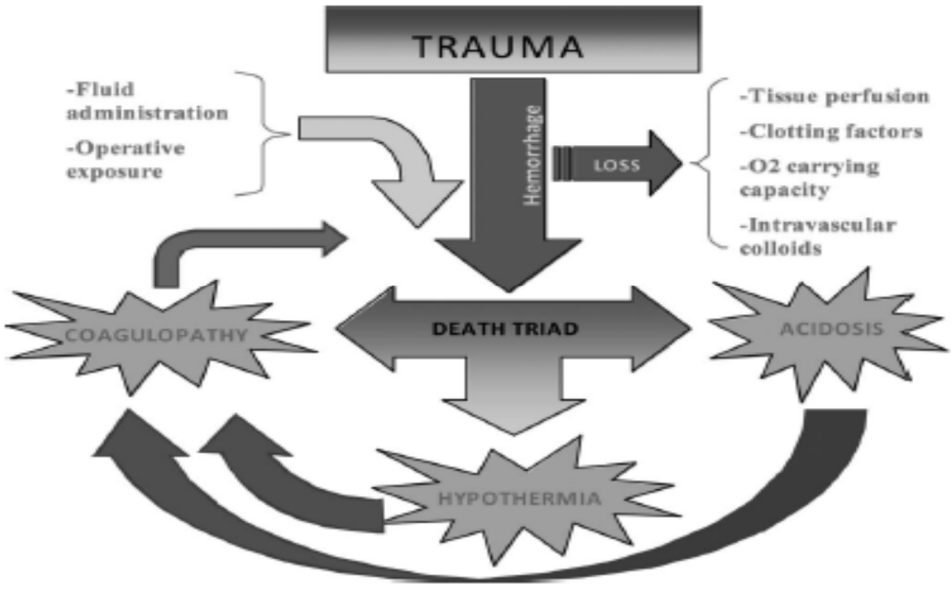

Figure (1): Components involved in the development of coagulopathy of trauma (Ganter and Pittet, 2010).

Hemodilution:

Dilution of coagulation factors and platelets is an important cause of coagulopathy in massively transfused patients **(Chappell *et al*., 2008).**

The Advanced Trauma Life Support guideline recommends aggressive crystalloid resuscitation but the dilutional effects of such administration on coagulation competence are well described and this strategy provokes acidosis, formation of interstitial oedema with tissue swelling, impairment of the microcirculation and hence compromised oxygenation ***(*Thorsen *et al*., 2011*).***

Also, administration of blood products such as red blood cells (RBCs), fresh frozen plasma (FFP) and platelets may cause significant dilution since these blood products are stored in anticoagulation solutions reducing coagulation factor concentration to approximately 60% and platelet count to approximately 80x109/l when a hematocrit of 30% is warranted **(Hess, 2008).**

Furthermore, synthetic colloid resuscitation fluids influence coagulation competence more profoundly than crystalloids **(Mittermayer *et al*., 2007).**

Hydroxyethyl starch (HES) causes efflux of plasma proteins from blood to the interstitial space, reduction in plasma concentration of coagulation factor VIII and von Willibrand factor (vWF), inhibition of platelet function and reduced interaction of activated FXIII with fibrin polymers **(Mittermayer *et al*., 2007).**

Hypothermia

Hypothermia is associated with risk of uncontrolled bleeding and death in trauma patients**.** Hypothermia induced coagulopathy is attributed to platelet dysfunction, reduced coagulation factor activity (significant below 33°C) and induction of fibrinolysis and these effects are reversible with normalization of body temperature **(Wolberg *et al*., 2004).**

Acidosis

Acidosis is often induced by hypoperfusion and excess administration of ionic chloride, i.e. NaCl during resuscitation **(Hess *et al.*, 2008).**

Acidosis impairs almost all essential parts of the coagulation process. At pH < 7.4, platelets change their structure and shape **(Etulain *et al*., 2012).**

The activity of coagulation factor complexes on the cell surface is reduced and the resulting impaired thrombin generation is a major cause of coagulopathic bleeding. Furthermore, acidosis leads to increased degradation of fibrinogen which further aggravates the coagulopathy **(Martini and Holcomb 2007).**

Consumption

Tissue injury secondary to trauma induce immediate activation of the coagulation system through upregulation of tissue factor (TF) expression and extensive thrombin generation**.**Tissue injury in association with extensive endothelial injury, massive soft tissue damage, and fat embolization from long bone fractures, may be associated with consumption of coagulation factors and platelets and, hence

development of coagulopathy**.** Disseminated intravascular coagulation (DIC) is the most extreme form of consumptive coagulopathy and is characterized by systemic activation of pathways leading to and regulating coagulation, which can result in the generation of fibrin clots that may cause organ failure with concomitant consumption of platelets and coagulation factors that may result in clinical bleeding **(Levi *et al*., 2009).**

It has been reported that DIC is not a part of the early coagulopathy secondary to trauma, but it may develop later in the course of resuscitation **(Johansson *et al*., 2011)**

Trauma and acute coagulopathy

The early "endogenous" coagulopathy in trauma patients not attributed to dilution, hypothermia with shock and acidosis as the key drivers of acute traumatic coagulopathy through widespread activation of the anticoagulant and fibrinolytic pathways **(Frith *et al*., 2012).**

Acute traumatic coagulopathy is due to systemic anticoagulation due to the activation of protein C pathway **(Brohi *et al*., 2007*).***