INTRODUCTION

Hemorrhage remains the primary preventable cause of death for patients presenting with severe trauma. Twenty-five per cent of patients with traumatic injury upon admission present with coagulopathy. This has recently been described as trauma-induced coagulopathy and has been demonstrated to increase the risk of hemorrhage and death in this population. This coagulopathy is complex and multifactorial: induced by tissue factor activation, endothelial injury, ischaemia, inflammation, and exacerbated by factor consumption, fibrinolysis, hypocalcaemia, haemodilution, hypothermia and acidosis ***(Spinella and Holcomb, 2009).***

The concept of hemostatic or damage control resuscitation is the optimal approach for the treatment of patients with severe life-threatening hemorrhagic traumatic injuries, This approach advocates for the rapid control of surgical bleeding, transfusion of RBCs, plasma, and platelets in a 1:1:1 ratio; preference for the use of fresh RBCs; limitation of excessive crystalloid use; and prevention of acidosis and hypothermia. The use of warm fresh whole blood (WFWB) would improve both short-term (24 hour) and 30-day survival when compared with patients transfused only stored component therapy in this population ***(Spinella and Holcomb, 2009).***

"Hypotensive" or "low-volume" fluid resuscitation has become increasingly accepted in the prehospital resuscitation phase of trauma, prior to definitive hemorrhage control, since aggressive fluid resuscitation may increase bleeding. Resuscitation after haemorrhage control is focused on restoration of tissue oxygenation ***(Napolitano,2005).***

Efforts to optimize resuscitation have used "resuscitation endpoints" as markers of adequacy of resuscitation. The resuscitation endpoints that have been evaluated include both global (restoration of blood pressure, heart rate and urine output, lactate, base deficit, mixed venous oxygen saturation, ventricular end-diastolic volume) and regional (gastric tonometry, near-infrared spectroscopy for measurement of muscle tissue oxygen saturation) measures ***(Napolitano,2005).***

THE AIM OF THE WORK

To discuss different strategies used in hemostatic resuscitation for traumatic hemorrhagic shock patient.

PATHOPHYSIOLOGY OF TRAUMATIC HEMORRHAGIC SHOCK

Traumatic Hemorrhagic Shock (THS):

It is defined as a state of inadequate organ perfusion for normal aerobic metabolism due to a loss of circulating blood volume. Hemorrhagic shock is the second most frequent cause of death in trauma patients and it is the leading cause of preventable death following penetrating or blunt injury ***(Coimbra, 2007).***

Pathophysiology of Traumatic Hemorrhagic Shock:

1. Systemic Effects of Blood Loss :

Hemorrhage initially results in a series of compensatory responses intended to maintain circulating blood volume. Decreased wall tension in large central arteries activates baroreceptors and leads to neural and hormonal adrenergic responses. The neural response acts rapidly, via sympathetic fibers from the stellate ganglion. Stimulation of sympathetic fibers leads to β1-receptor activation and increased heart rate and contractility. These changes also lead to increased myocardial oxygen demand and eventual myocardial dysfunction if myocardial oxygen supply becomes insufficient ***(Guyton and Hall, 2001).***

Also, peripheral sympathetic stimulation occurs via α1-receptors on peripheral arterioles and leads to vasoconstriction. About 70% of the circulating volume of the blood is contained within the venous system, and sympathetic stimulation reduces the capacity of the venous system to increase venous return to the central circulation. The selective regional nature of the vasoconstriction maintains brain and heart perfusion at the expense of blood flow to the skin, skeletal muscle, gut, and kidneys. Regional vasoconstriction in early hemorrhagic shock reduces perfusion first to skeletal muscle and abdominal viscera. Despite the presence of local fuel substrates in these tissues, it is the lack of oxygen delivery that impairs the operation of the tricarboxylic acid cycle in the mitochondria and results in a build-up of pyruvate, which is converted to lactate, then rapidly transported out of the cell. Production of lactate is a hallmark of anerobic metabolism and it is an important plasma marker of inadequate organ perfusion ***(Guyton and Hall, 2001).***

The hormonal adrenergic response occurs via the hypothalamic–pituitary–adrenal axis which is responsible for the release and secretion of stress hormones, including epinephrine and norepineprhine from the adrenal medulla, corticocosteroids from the adrenal medulla, renin from the kidney, glucagon from the pancreas, and vasopressin from the pituitary. Other vasoactive compounds released into the

circulation during the shock state include bradykinin, histamine, prostanoids, and cytokines. This rush of chemicals sets the stage for the microcirculatory responses that follow ***(Coimbra, 2007).***

2. Effects of Blood Loss on Cellular Perfusion:

Cells within inadequately perfused tissue will eventually deplete their adenosine tri-phosphate (ATP), resulting in the loss of the normal cell membrane electrical gradient and cell wall integrity. Loss of the membrane gradient results in sodium, water, and calcium entry into the cell, leading to cell swelling. ATP depletion also impairs enzyme and protein production, intracellular signal transduction, and DNA repair ***(Coimbra, 2007).***

Unchecked, the process becomes irreversible and cell death will occur by necrosis. Cell death can also occur by apoptosis. Apoptotic cell death of lymphocytes and gut epithelial cells has been detected in trauma patients within three hours of injury ***(Hotchkiss et al., 2000).***

3. Effects of Blood Loss on the Activation of Immune Cells:

Evidence suggests that an initial insult (hemorrhage or massive injury) primes the immune system, which then becomes over stimulated following a second insult (fluid resuscitation or blood transfusion), leading to MODS. This

paradigm illustrates the ‘two-hit’ theory of hemorrhage and the interplay of the immune system in MODS and late death. In this regard, the two-hit paradigm challenges the notion that periods of shock are responsible for tissue damage following hemorrhage; instead, reperfusion and the subsequent activation of the immune system may be the most significant factor ***(Coimbra, 2007).***

The immune response after trauma and hemorrhage is a complex interplay of cellular and molecular events involving catecholamines, hormones, and cytokines. It is perhaps easiest to consider acute hemorrhage as a global inflammatory state with specific pro-inflammatory cytokines acting as potent mediators. Pro-inflammatory cytokines, specifically tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-3, and IL-6 begin to circulate rapidly after injury and hypotensive states. Central to post-trauma immune activation and cytokine production is the role of the polymorphonuclear neutrophil. Neutrophils are recruited to inflammatory sites and constitute the first line of host defense. Following acute hemorrhage, neutrophils migrate into tissues via surface adhesion molecules (CD11b/CD18) interacting with endothelial-binding proteins (ICAM-1) After migration, a series of immunological functions occurs, including phagocytosis, oxidative burst, further production of pro-inflammatory cytokines, and bactericidal activity ***(Coimbra, 2007).***

Resuscitation Injury:

However, an exaggerated inflammatory response – stimulated by massive crystalloid resuscitation and blood transfusion - may initiate neutrophil migration into surrounding parenchyma, where an intense, inflammatory response occurs releasing free radicals and resulting in neutrophil-mediated tissue injury. An overwhelming activation of the inflammatory cascade can lead to hemodynamic collapse, ARDS MODS, and, ultimately, death. Therefore, hemorrhage mortality can be directly related to both exsanguination and resulting inflammatory and immunologic processes. In other words, trauma is an immune disease ***(Coimbra, 2007).***

Large-volume crystalloid resuscitation has other harmful effects, including gastrointestinal and cardiac complications, increased extremity compartment pressures, and coagulation disturbances. Abdominal compartment syndrome is the only complication clearly proven to be a result of large-volume crystalloid resuscitation. Primary abdominal compartment syndrome, which results from severe, direct abdominal injury, has been understood for years. Secondary abdominal compartment syndrome occurs in patients without any underlying abdominal injury, has mortality greater than 50%, and is clearly linked to over aggressive fluid resuscitation strategies ***(Cherkas, 2011).***

4. Occult Hypoperfusion:

Occult hypoperfusion (inadequate organ and tissue perfusion in the presence of normal or relatively normal vital signs) can be identified through a careful physical examination plus an evaluation of metabolic markers of tissue hypoperfusion . Patients should be examined for physical manifestations of poor perfusion, such as cool and clammy skin, mental status changes, and decreased urine output. Metabolic markers of hypoperfusion include bicarbonate, base deficit, and lactic acidosis. With inadequate perfusion, cells will begin anaerobic metabolism and generate lactic acid as well as other acidic by-products ***(Cocchi et al., 2007).***

Several investigators have recently described the existence of occult hypo perfusion in the trauma patient. A study of patients with penetrating abdominal trauma who had normal hemodynamics upon presentation and were taken to the operating room for laparatomy. And despite seemingly reassuring vital signs, a number of these patients had a significant amount of intra-abdominal hemorrhage ***(Brown et al., 2005).***

Recently a study validated the clinically accepted concept that hypotension is a late sign of shock. In this study, systolic blood pressure did not decrease to less than 90 mm Hg until the base deficit was worse than (-20), with mortality

reaching 65%. These findings illustrate that significant pathology and hypoperfusion can be present in the normotensive patient, and that tissue hypoperfusion precedes hypotension in many patients ***(Parks et al., 2006).***

Occult hypoperfusion may be particularly concerning in the elderly as well, A study reported a mortality of 38% in normotensive elderly trauma patients with initial lactic acid levels of more than 4mmol/dL.Thus, the use of lactic acid and base deficit can serve as metabolic markers of tissue hypoperfusion and should serve as adjuncts to a careful history and physical examination ***(Callaway et al., 2007).***

5. Trauma-Induced Coagulopathy:

Massive hemorrhage after traumatic injury is frequently a combination of surgical and coagulopathic bleeding ***(Tein et al., 2007).*** While bleeding from vascular injury can usually be repaired surgically, coagulopathy-related bleeding is often more difficult to manage and may also mask the site of vascular injury ***(Spahn and Rossaint, 2005).*** The coagulopathy of trauma is a syndrome of non-surgical bleeding from mucosal Lesions, serosal surfaces, wound and vascular access sites ***(Hess and Lawson, 2006).***

Major causes of coagulopathy in trauma patients are:

1- Blood loss.

2- Consumption of platelets and coagulation factors.

3- Dilution of coagulation factors and platelets.

4- Increased fibrinolysis.

5- Impaired functions of platelets and coagulation factors.

6- Coagulation-compromising effect of colloids.

7- Hypothermia.

8-Hypocalcaemia.

(Spahn &Rossaint,2005)

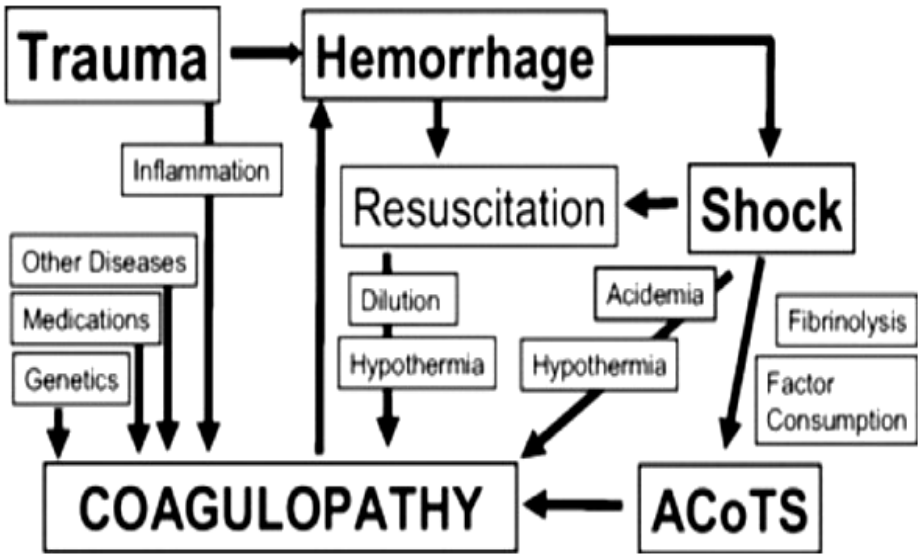

Figure 1: Diagram showing some of mechanisms leading to coagulopathy in the injured. ACoTS = Acute Coagulopathy of Trauma-Shock ***(Dries, 2010).***

I- Consumption Coagulopathy:

Hemorrhage in trauma patient cause activation of the coagulation and fibrinolytic systems which results in the consumption of platelets and coagulation factors, and continuing bleeding causes further depletion of these haemostatic constituents from the circulation ***(Spahn and Rossaint,2005).***

II- Decreased Levels of Coagulation Factors and Platelets:

Infusion of large volumes of crystalloid and colloid during resuscitation reduces the concentrations of platelets and coagulation factors. In addition, thrombocytopenia is seen commonly in patients who have received massive blood transfusion, and has been thought to be a major cause of coagulopathy. Although platelets are present in whole blood, storage at 4°C severely damages them and the remaining platelets disappear from the circulation almost immediately after transfusion ***(Spahn and Rossaint, 2005) .***

In current practice, RBCs in additive solution rather than whole blood are widely used. Consequently, RBC units contain negligible amounts of coagulation factors and platelets, and thrombocytopenia and subnormal levels of coagulation factors often occur at an early stage during massive RBC transfusion ***(Spahn and Rossaint, 2005).***

The increased acid load from RBC units may also contribute to coagulopathy. The pH of an RBC unit is low, and decreases progressively during storage, due to the production of lactic acid by RBCs, from around 7.0 initially to around 6.3 at the end of its shelf-life. Because of the high buffering capacity of plasma in the circulation, transfusion of RBCs with such low pH does not usually cause acid–base disturbance. However, in the case of trauma patients who are already acidotic, massive transfusion of RBCs further increases the acid load, which may in turn exacerbate the ongoing coagulopathy ***(Armand and Hess, 2003).***

III- Increased Fibrinolysis:

It results from blood loss, hypovolemia-induced activation of the protein C system and consequent increase of the fibrinolytic potential ***(Fries et al., 2009).*** An increase in thrombomodulin induced by hypoperfusion would divert thrombin from fibrin generation to the activation of Protein C, leading to anti-coagulation and inhibition of Further thrombin generation ***(Brohi et al., 2007).***

IV- Hypothermia:

The causes of hypothermia are multifactorial and Interdependent, including altered central thermoregulation, decreased heat production due to tissue hypoperfusion in haemorrhagic shock, exposure to low ambient temperature, and

infusion of inadequately warmed resuscitation fluids and blood components ***(Spahn and Rossaint, 2005).***

V- Metabolic Acidosis:

Under conditions of cellular hypoxia metabolic acidosis is due to the formation of hydrogen ions during ATP hydrolysis that are not reused for the formation of ATP, due to the absence of available oxygen ***(Handy, 2007).***

Hypothermia and acidosis compromise thrombin-generation kinetics via different mechanisms. Hypothermia primarily inhibits the initiation phase, whereas acidosis severely inhibits the propagation phase of thrombin generation. Similarly, hypothermia and acidosis affect fibrinogen metabolism differently. Hypothermia inhibits fibrinogen synthesis, whereas acidosis accelerates fibrinogen degradation, leading to a potential deficit in fibrinogen availability. In addition, coagulation complications caused by acidosis cannot be immediately corrected by PH neutralization alone ***(Martini, 2009).***

The interrelationship between hypothermia, metabolic acidosis and progressive coagulopathy is referred to as the "lethal triad"; each factor exacerbates the others, leading to life threatening bleeding or exsanguinations ***(Spahn and Rossaint, 2005).***

VI- Hypocalcaemia:

The availability of ionised calcium is essential for the timely formation and stabilisation of fibrin polymerisation sites, and a decrease in cytosolic calcium concentration precipitates a decrease in all platelet-related activities ***(Lier et al., 2008).***

Acute traumatic coagulopathy (ATC) is a frequent complication of severely injured Patients. As, about one-third of all trauma patients with bleeding present with a coagulopathy on hospital admission. This subset of Patients has a significantly increased incidence of multiple organ failure and death compared to patients with similar injury patter ns in the absence of coagulopathy. So, early identification and subsequent management of trauma induced coagulopathy will help improve outcome in trauma patient with hemorrhagic shock ***(Rossaint et al., 2010).***