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Review Article

The challenge in management of hemorrhagic shock in trauma

Col Mathews Jacob^{a,*}, Praveen Kumar^b^a Associate Professor, Department of Anaesthesiology and Critical Care, Armed Forces Medical College, Pune 411040, India^b Resident, Department of Anaesthesiology and Critical Care, Armed Forces Medical College, Pune 411040, India

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ABSTRACT

Transfusion and resuscitation practices in trauma have undergone a sea change over the past decade. New understanding of transfusion physiology and experiences in military trauma over the last decade has identified key factors taken as challenges in trauma. The most important challenge remains acute traumatic coagulopathy (ATC) which sets in early after a trauma and spirals the patient into shock and continued bleeding. World wide trauma is the leading cause of mortality. More than 6 million deaths occur due to trauma out of which 20% are due to uncontrollable bleeding. Out of the hospital admissions in trauma 20% develop coagulopathy. Mortality is three to four times higher in a patient with coagulopathy and thus prevention and correction of coagulopathy is the central goal of the management of hemorrhagic shock in trauma. Damage control resuscitation (DCR), a strategy combining the techniques of permissive hypotension, hemostatic resuscitation and damage control surgery has been widely adopted as the preferred method of resuscitation in patients with haemorrhagic shock. The over-riding goals of DCR are to mitigate metabolic acidosis, hypothermia and coagulopathy. This article looks at the importance of acute traumatic coagulopathy, its etiology, diagnosis, effects and resuscitation strategies to prevent it and to see the background behind this shift.

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Introduction

Every year, around 5.8 million people die worldwide due to events related to trauma, which corresponds to about 9.7 per 100000 population making trauma one of the leading cause of death and disability in all age groups in both sexes. About 40% of trauma related deaths are due to hemorrhage or its consequences.¹

Outcomes from severe hemorrhage remains poor, with mortality rates approaching 50% for patients requiring blood transfusion, or for those who develop a significant coagulopathy.² On an average one in every four patient who is severely injured has acute trauma related coagulopathy at the time of admission to the emergency room.²

Researchers over the years have proved that coagulopathy relating to trauma plays a major role in determining the morbidity and mortality in trauma patients.³ This high degree

* Corresponding author. Tel.: +91 9049498131 (mobile).

E-mail address: drmathewsjacob@yahoo.com (M. Jacob).<http://dx.doi.org/10.1016/j.mjafi.2014.03.001>

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of morbidity and mortality can be reduced by early detection of acute traumatic coagulopathy followed by early damage control resuscitation.

Acute traumatic coagulopathy

Coagulopathy following trauma is multifactorial, involving various components of the coagulation system. Endothelium, platelets, fibrin activation and dysfunction, fibrinolytic pathways; all play a crucial role. Which of these mechanisms predominates, depends on the severity of trauma. There appear to be six main initiators of acute traumatic coagulopathy: 1. Tissue injury 2. Shock – hypoperfusion 3. Hemodilution 4. Hypothermia 5. Acidosis and 6. Inflammation.

Tissue injury

All traumatic injuries invariably lead to tissue damage although the severity of tissue injury varies widely. Crush injuries are associated with maximum tissue damage. The severity of the injury closely correlates with the degree of coagulopathy.² Tissue injury leads to activation of both clotting and fibrinolytic systems. Endothelial tear and damage which occurs due to tissue trauma leads to activation of coagulation system as the injury leads to exposure of tissue factor and subendothelial collagen type III, which activates coagulation proteases leading to thrombin and fibrin formation at the site of exposure.

Polytraumatic injury results in tissue factor (TF) thromboplastin release from damaged cells. Acute coagulopathy of trauma (ACT) occurs early and results from tissue hypoperfusion and the tissue injury. Coagulopathy associated with traumatic brain injury (TBI) results from the interplay of various factors. Because of the high concentration of tissue factor in the brain tissue, TBI has been believed to be associated with a greater degree of coagulopathy compared with injury in other body systems.⁴

Hypoperfusion

A central role in the emergence of acute traumatic coagulopathy is thought to be played by hypoperfusion resulting due to shock and hypotension.⁵ There is a direct correlation between the degree of hypotension and the laboratory derangements in the coagulation profile.

Hypoperfusion in trauma patients is associated with a moderate, dose-dependent reduction in the activity of coagulation factors II, VII, IX, X, and XI, and a more pronounced reduction in factor V activity, which is relatively independent of the severity of shock. The mechanisms underlying decreased factor V activity may be due to activated protein C mediated cleavage.⁵

Markers of hypoperfusion, such as base deficit, might be better and more readily available predictors of who all require coagulation support than international normalized ratio or activated partial thromboplastin time.

Hemodilution

Hemodilution leads to dilution of coagulation factors leading to significant amount of coagulopathy post trauma. During trauma and shock, there is a fall in intravascular hydrostatic pressure which leads to shift of fluid from interstitial and intracellular spaces into the intravascular compartment leading to significant reduction in coagulation factors.³ This resultant hemodilution is compounded by the administration of crystalloids and colloids.

Hypothermia

Hypothermia is usually observed in trauma patients due to environmental exposure, reduced heat production from underperfused tissues, excessive losses, administration of cold fluids and blood products.⁶ Clinically significant levels of reductions in platelet function, aggregation and enzyme activity occur at core body temperatures of 33 °C and below.⁷ Drop in temperature by 1 °C is associated with a 10% drop in platelet function.

The activity of tissue factor or FVIIa complex reduces linearly with temperature. The activity is reduced to about 50% at temperatures of 28 °C. At low temperatures, the attraction between von Willebrand factor is reduced causing defective platelet adhesions. However, within the temperature range of 33–36 °C which is usually seen in trauma patients, hypothermia in isolation rarely affects the coagulation system.⁸

Acidosis

Because of hypotension and hypoperfusion which are seen in trauma, there is a significant acidemia in the patient which is further compounded by excessive administration of chloride containing fluids. Fall in pH by itself impairs the function of plasma proteases.

A decrease in pH from 7.4 to 7.0 reduced the activity of FVIIa by over 90% and that of FVIIa/Tissue factor by over 60%.⁹ Administration of buffer solutions to correct acidosis have not been shown to correct the coagulopathy that has already set in, indicating that acidosis does not merely reduce the coagulation protease activity.

Inflammation

Massive injury leads to activation of the immune system and the initial inflammatory immune response and has been defined as systemic inflammatory response syndrome (SIRS). This initial response is usually compounded by secondary insults like infections, ischemia/reperfusion or surgeries.¹⁰ Inflammation shifts the hemostatic mechanisms in favor of thrombosis. Multiple mechanisms are at play including upregulation of tissue factor leading to the initiation of clotting, amplification of the clotting process by augmenting exposure of cellular coagulant phospholipids, inhibition of fibrinolysis by elevating plasminogen activator inhibitor1 and decreases in natural anticoagulant pathways, leading to downregulation of the protein C anticoagulant pathway. The decreased function of the natural anticoagulant pathways may be particularly problematic because

these appear to play a role in dampening the inflammatory responses.¹¹

Activation of serine proteases can cause inflammation through cell surface receptors and activation of the complement system.

Detection of acute traumatic coagulopathy

Routine tests for coagulation

Routine practice to detect trauma induced coagulopathy has been by various parameters like INR (International Normalized Ratio), APTT (Activated Partial Thromboplastin Time), platelet counts and fibrinogen levels.

APTT and INR >1.5 times are considered as indicators of coagulopathy as it is often assumed that the conventional coagulation screens (INR and APTT) monitor coagulation; however, these tests monitor only the initial phase of blood coagulation and represent only the first 4% of thrombin production.¹² It is therefore possible that the conventional coagulation screen appears normal, while the overall state of blood coagulation is abnormal. Another important short coming of the standard coagulation tests is that these tests are time consuming. Median turnaround time of 78–88 min has been reported in various studies.^{13,14}

Thromboelastography (TEG)

Described by Hartert in 1948, thromboelastography is now widely used as a point of care tool to detect acute coagulopathy of trauma. It gives a rapid overview of the main players in the coagulation system like initiation factors, fibrinogen, platelet function and fibrinolytic components.¹⁵

A small volume of blood (0.3 ml) is incubated in an oscillating cup at 37 °C or patients body temperature. A pin is suspended in the cup from a torsion wire with an electrical transducer. In the early phase when, there is no clot the oscillatory movements of the cuff do not affect the suspended pin. When a clot is formed, the fibrin which is formed between the cup and pin transmits the movements which can be detected at the pin and a trace is generated. (The various interpretations are described in Fig. 1 and Table 1).

Though thromboelastography has emerged as a point of care device in identifying coagulopathy in acute trauma, it has important limitations. Studies have found that

thromboelastography was unable to distinguish coagulopathies caused by hemodilution from that caused by thrombocytopenia thereby leading to unwarranted platelet transfusions. This limitation is overcome by the advent of thromboelastometry. Another significant limitation of viscoelastic tests is the lack of sensitivity to detect and monitor platelet dysfunction due to antiplatelet drugs. The view that the effect of hypothermia will not be recognized if the temperature of the blood sample analyzed is not adjusted to patient's body temperature is no longer supported.

The widely available devices for rapid detection of coagulopathy are TEG 5000 (thromboelastography) analyzer and ROTEM (rotational thromboelastometry).

Resuscitation in acute traumatic coagulopathy

There has been a marked shift in the practice of trauma resuscitation over the last decade, towards damage control resuscitation following the changes in our understanding of acute traumatic coagulopathy. Damage control resuscitation employs multiple strategies to combat hypothermia, acidosis, hypoperfusion and coagulopathy. Techniques include active rewarming, restricting fluid administration, aggressive early blood products administration in an effort to prevent and limit acute traumatic coagulopathy. Various recommendations have been published in recent times for the management of coagulopathy of trauma. Most of them emphasize on assessment of shock and tissue hypoperfusion, rapid detection and quantification of coagulopathy, and damage control resuscitation. We propose the following steps of damage control resuscitation for prevention and treatment of acute traumatic coagulopathy which is the result of experience gained in the last decade and based on recent evidences. Recommendations were formulated and graded according to the grading of recommendations assessment, development and evaluation (GRADE) hierarchy of evidence (summarized in Table 2).

Control of bleeding

Use of tourniquet

Tourniquet is to be applied in case of life threatening hemorrhage from the extremities in pre surgical settings (Grade

Fig. 1 – TEG trace.

Table 1 – TEG interpretation (explanation of Fig. 1).

Parameter	TEG	Interpretation
Clotting time Period to 2 mm amplitude	R (reaction time)	Represents initiating clotting factors
Clot kinetics Period from 2 to 20 mm amplitude	K (kinetics) Alpha – slope between R&K	Measure of fibrinogen concentrate
Clot strength	MA (max amplitude)	Measure of platelet function
Clot lysis Lysis at fixed time	Ly30	Measure of rate of fibrinolysis

Table 2 – Grading of recommendation.

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C Strong recommendation, low-quality or very low- quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C Weak recommendation, Low-quality or very low- quality evidence	Uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be closely balanced	Observational studies or case series	Very weak recommendation; other alternatives may be equally reasonable

1B). Tourniquet should be left in place till the surgical control of bleeding is achieved albeit this time should be reduced to less than 6 h in order to prevent complications associated with tourniquet like nerve paralysis and acute limb ischemia.^{16,17}

Surgical control of bleeding

Surgical control of bleeding should be considered in patients with uncontrolled hemorrhage presenting with haemorrhagic shock with identified source of bleed (Grade 1B) and the time for this should be minimized in order to prevent mortality related to trauma as more than 50% of all trauma patients with a fatal outcome die within 24 h of injury.¹⁶

Local hemostatic agents

Use of local hemostatic agents like collagen, gelatin and cellulose based products, fibrin and synthetic glues should be considered along with other surgical methods in patients with blunt trauma abdomen presenting with parenchymal injuries and associated uncontrolled hemorrhage (Grade 1B).^{16,18}

Further assessment

Patients presenting with haemorrhagic shock with unidentified source of bleeding should undergo rapid examination by Focused assessment with sonography for trauma (FAST) in order to detect the source of bleeding (Grade 1B).¹⁹ FAST is a rapid study utilized to identify hemorrhage. In FAST ultrasound technology is used by properly trained individuals to detect the presence of haemoperitoneum. With specific equipment and experienced hands, ultrasound has a sensitivity, specificity, and accuracy in detecting intra-abdominal fluid comparable to direct peritoneal lavage

(DPL). Thus, ultrasound provides a rapid, noninvasive, accurate, and inexpensive means of diagnosing haemoperitoneum that can be repeated frequently. Furthermore, ultrasound can detect one of the nonhypovolemic reasons for hypotension: pericardial tamponade. Scans are obtained of the pericardial sac, hepatorenal fossa, splenorenal fossa and pelvis or pouch of Douglas. Patients who are hemodynamically stable should be further assessed by use of CT scans (Grade 1B).¹⁶

Shock-hypoperfusion

Serum lactate and base deficit measurements are excellent predictors to assess the severity of bleeding, resultant shock and hypoperfusion. Changes in lactate concentrations have been shown to provide an early and objective evaluation of a patient's response to therapy and repeated lactate determinations have proved to be a reliable prognostic index for patients with hemorrhagic shock.²⁰ Early return of lactate levels to normal levels (<2 mmol/l) within 24 h has been proved to be associated with improved outcomes in terms of mortality. A significant correlation has been established between the admission base deficit and transfusion requirements within the first 24 h and the risk of post-traumatic organ failure or death.²¹

Fluid resuscitation to correct shock

Crystalloids should be used to correct shock with a target mean arterial pressure of not more than 65 mmHg in patients with no evidence of traumatic brain injury (Grade 1A). Higher blood pressure targets requiring large volumes of

fluid may increase hydrostatic pressure, thereby dislodging the clot, can produce dilution coagulopathy and make the patient cold which could be detrimental. The incidence of coagulopathy has been found to increase by 40% in patients receiving 2 L of fluid to about 70% in patients receiving 4 L of fluids.²² It is prudent to limit use of fluids to small aliquots of 250 ml of crystalloids (Ringer Lactate) to keep the radial pulse palpable (systolic blood pressure > 80 mmHg) and the patient conscious and oriented. In a patient with traumatic brain injury (TBI), a higher systolic blood pressure of 100 mmHg is recommended to maintain the cerebral perfusion pressure. Colloids should be used within its prescribed limits in patients who are hemodynamically unstable as the colloid solutions notably starch based solutions can precipitate coagulopathy and renal failure. Hypertonic saline may have a role in traumatic brain injury (TBI).

Assessment of coagulation

Conventional coagulation screens which include INR, APTT, Platelet counts, Fibrinogen levels and assessment of initial clotting factors, clot strength, fibrin concentrate, platelet function and the rate of fibrinolysis should be assessed by thrombelastography. An increase in INR and APTT of more than 1.5 times and 5 min clot amplitude of less than 36 mm on thromboelastography (TEG) is diagnostic of acute traumatic coagulopathy.

Blood and blood products

Packed red blood cell (PRBC) and fresh frozen plasma (FFP)

In order to maintain tissue oxygen delivery and restore an effective coagulation, early administration of PRBCs and fresh frozen plasma is recommended (Grade 1B). The administration of red blood cells is considered indispensable when the Hb levels are less than 7 g%.

The administration of fresh frozen plasma should be as early as possible with transfusion of PRBCs in order to compensate for the deficit in coagulation factors and also to prevent dilutional coagulopathy. FFP transfusion is recommended when APTT and INR are 1.5 times the normal. The most frequently recommended initial dose is 10–15 ml/kg and further doses should be based on coagulation parameters.

Though several recent studies have highlighted the importance of high PRBC:FFP ratio (ratio of approximately 1:1), these studies have a potential for survival bias (patients who have died early are more likely to have received a higher PRBC:FFP ratio). Thus the optimal value of PRBC:FFP ratio remains controversial. Because FFP requires a significant amount of time before it is thawed and available for transfusion and many trauma deaths occur soon after hospital admission, patients who die early may receive RBC units but die before FFP therapy has begun. The PRBC:FFP ratio is an important element in early PRBC and FFP transfusion, but the time at which the FFP transfusion

has begun would determine the outcome in terms of mortality rather than the ratio of PRBC to FFP.^{23,24} The role of whole blood is limited to the military setting where walking blood banks are created. In civilian practice whole blood has no role due to the concern of transmission of viral infections.

Platelet transfusion

Platelets should be transfused to maintain a blood platelet count of more than 50,000/cumm in trauma patients and more than 100,000/cumm in patients with traumatic brain injury (Grade 1C).²⁵

Fibrinogen concentrate and cryoprecipitate

As a precursor of clot formation, fibrinogen plays a major role in coagulation function. Fibrinogen deficiency is linked to uncontrolled bleeding and compromised survival. Hypofibrinogenemia is an important part of trauma associated coagulopathy. The use of fibrinogen concentrate and cryoprecipitate is recommended when the plasma fibrinogen level falls below 1.5–2.0 g/l or when there is a thromboelastometric evidence of functional fibrinogen deficiency (Grade 1C).¹⁶ An initial fibrinogen concentrate dose of 3–4 g or 50 mg/kg of cryoprecipitate, which is approximately equivalent to 15–20 units in a 70 kg adult and further doses based on thromboelastometric analysis is recommended (Grade 2C).¹⁶

Antifibrinolytics

Hyperfibrinolysis is an important contributor to trauma induced coagulopathy. Fibrinolysis greater than 3% as measured by thromboelastometry is the critical value for initiation of antifibrinolytic therapy.²⁶ Tranexamic acid has been found to reduce the transfusion requirements and improve mortality in trauma patients.^{16,27} The use of tranexamic acid with a loading dose of 1 g over 10 min followed by 1 g over 8 h is recommended (Grade 1A). The use of drug in the early period within 3 h of trauma has been found to be beneficial and no improvement in outcome has been found when used after 3 h.²⁷

Role of recombinant factor VIIa (rFVIIa)

Recombinant factor VIIa is not the first line treatment in bleeding trauma patients. Since FVIIa acts on patient's own coagulation system, there must be adequate number of platelets and fibrinogen levels available for it to cause thrombin burst.²⁸ The efficacy of rFVIIa as a pro-hemostatic agent and to stop bleeding also varies widely with the physiological state of the body like core body temperature and acidosis. Decrease in body temperature up to 33 °C has been found to have very little impact on the effectiveness of rFVIIa, but with further fall in body temperature there is a linear reduction in the activity of FVIIa. At temperatures of 28 °C and below, its activity falls by more than 50%. In severe metabolic acidosis as seen in bleeding trauma patients the activity of rFVIIa is highly affected. At a pH of 7.0, the activity is reduced

by 90%. Therefore rFVIIa should be considered only after adequate resuscitation, normalization of platelet and clotting factor concentration, and in the absence of hypothermia and acidosis (Grade 2C).¹⁶

Correction of hypothermia

Steps to prevent hypothermia and the risk of hypothermia-induced coagulopathy include removing wet clothing, covering the patient to avoid additional heat loss, increasing the ambient temperature, forced air warming, warm fluid therapy and, in extreme cases, extracorporeal re-warming devices.²⁹

Anti-inflammatory agents

Severe tissue injury is characterized by an intense inflammatory response leading to a systemic inflammatory response. Various drugs that decrease inflammation like recombinant human activated protein C (APC), IL-1 receptor antagonist, anti-TNF and anti-LPS agents are not found to be effective in bleeding trauma patients. Albeit steroids have been found to reduce the incidence of pneumonia and the number of ventilator free days, however recent studies have shown that there is no clear benefit in terms of mortality in these patients and may even be harmful in patients with traumatic brain injuries.³⁰

Conclusion

Management of trauma patients with haemorrhagic shock and acute traumatic coagulopathy is complex and difficult and remains a challenge. In spite of better understanding of pathophysiology of the events leading to acute traumatic coagulopathy, the mortality associated with it remains high. The role of the treating physician is, to identify the source of bleeding and achieve rapid control of bleeding by various measures. The main objective then would be to follow damage control resuscitation guidelines by maintaining tissue oxygenation, proper and judicious use of volume expanders. Early use of blood and blood products is to be encouraged in order to prevent development of acute traumatic coagulopathy. The key would remain prevention, detection and early management of acute traumatic coagulopathy.

Conflicts of interest

All authors have none to declare.

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