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REVIEW ARTICLE

Hemostatic Coagulation Management in Trauma

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Abstract

Trauma is still a leading cause of death in the 21st Century mainly due to uncontrolled hemorrhage. Trauma has also an increasing cost of treatment in patients. Recently we have been aware of the importance of complex hemostatic and immunoinflammatory responses in pathogenesis of "Trauma Induced Coagulopathy". As a result of understanding of changes on coagulation pathway in trauma, different hypotheses put forward explaining the trauma induced coagulopathy. New treatment algorithms also take place in early coagulation management of patients with traumatic coagulopathy. In this review, we aimed to explain pathophysiological determinant of trauma induced coagulopathy and recent evidence-based hemostatic treatment approach for patients with trauma.

Keywords

Trauma, Coagulopathy, Mortality

Introduction

Annually, 5 million people lose their lives due to trauma. While 15% of deaths occur because of bleeding within the first 15 minutes, 35% of deaths occur within the first 2 hours [1]. Trauma Induced Coagulopathy (TIC) is seen in approximately 25-30% of trauma patients, making a 4-fold increase in mortality. Eighty percent of these patients die in the operation room due to active hemorrhage. Moreover, the cost of trauma-related procedures is high; nearly $38,628 per patient depending on the type of the surgery. Trauma related coagulopathy occur in 25-30% of trauma patients with 4 fold increased risk of mortality [2].

In recent years, changes, such as 'new type endothelium development' caused by trauma-induced hemorrhagic shock, have been widely understood and are thought to not only result in the damaging of the vascular structure, but also impairs the integrity of the coagulation-inflammation-blood/organ barrier and vasoregulation [2].

Cell-based Model of Thrombin Generation

Trauma leads to coagulopathy through blood loss and ischemia. Resulting cellular stress not only causes the release of toxins such as lactate, but also releases inflammatory mediators. As long as it is not intervened, multi-organ failure (MOF) and death occur as a result of apoptosis and necrosis.

Hemostasis is a natural defense mechanism induced by vascular damage and hemorrhage and a multiple-phase process involving both the cellular and humoral elements of coagulation. The aim is to ensure clotting. Roberts, et al. [3] indicated the cell-based model of thrombin generation during hemostasis.

The typical cell-based coagulation pathway takes place in the following steps:

1. Initiation: In case of trauma a tissue factor results from tissue damage and binds to F7a. Subsequently, this complex activates F10a and 5a. In this way, small amounts of thrombin form from prothrombin and activate platelets.

2. Amplification and activation: The platelets in the damaged area bind to fibrinogen generated and activation occurs with the transformation of the anatomy. von Willebrand factor separates from its complex with F8 complex, leading F8 to be activated. A small thrombin is generated.

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3. Propagation: F8 and F9 combine and form the tenase complex. F9 diffuses over the platelet surface and combines with the F5a and F10a bound to the platelet membrane to form the prothrombinase complex. In this way, large amount of prothrombin is generated, ensuring the formation of fibrin from fibrinogen.

The reason why no clot formation occurs under normal conditions is the suppression of platelet activation via nitrous oxide (NO) and prostacyclin secretion and the tight regulation of the fibrinolytic system by the activation of protein C and S anticoagulant enzymes. Furthermore, the amount of fibrinogen, vWF and platelets available in the environment are also a limiting factor. This whole balance is affected by pH-temperature-liquid resuscitation and Starling forces.

Definition of TIC

Traumatic coagulopathy is a condition in which complex hemostatic and immunoinflammatory responses, rather than damage-induced loss of blood and coagulation proteases, cause abnormal clot formation and the activation of anticoagulant pathways. It may course with hypo- or hypercoagulability depending on the response of the vascular bed. The main triggering factor is the global impairment of hemostasis caused by coagulation, inflammation and cellular dysfunction. The characteristic features include dysfibrinogenemia, hyperfibrinolysis, endotheliopathy, and impaired platelet activity. Glycocalyx degradation, the increase of thrombomodulin, autoheparinization, uncontrolled tPA formation and hyperfibrinolysis result in reduced clot formation. All these factors lead to vascular leak, tissue edema, microthrombus formation, impaired organ perfusion and ultimately uncontrolled hemorrhage.

Formation Mechanism

The mechanism may be evaluated in two classes: endogenous and iatrogenic [4]. Tissue trauma causes hemorrhage. Subsequently, the developing hypoperfusion results in hypothermia, endothelial activation, endogenous anticoagulation, and oxidation and acidosis due to ROS. Thus, platelet dysfunction occurs, platelet aggregation decreases and coagulation proteins are inactivated. At the same time, there is a decrease in the factors 2, 5, 7, 9, 10, 11, and PAI-1 along with the fibrinogen level. Hyperfibrinolysis increases tPA while decreasing the PAI-1 and TAFI levels. Iatrogenic TIC, on the other hand, develops during resuscitation performed due to hemorrhage. Its major causes are anticoagulant treatment and hemodilution. There are three different hypotheses explaining the TIC development phases.

Hypothesis 1

Thrombosis is triggered by the release of the tissue factor normally present in the tissue into circulation following trauma. Since neutrophil elastase degrades the tissue factor pathway inhibitor (TFPI), the tissue factor increases in an uncontrolled manner. Platelet signaling subsequently takes place. As a result of uncontrolled coagulation, the coagulation factors, particularly FI and FV, start to run out. Additionally, the release of tPA in the circulation and the formation of plasmin from plasminogen also stimulates fibrinolysis. In other words, while there is an extensive hypercoagulation, this situation stimulates hypocoagulation and bleeding because of the depletion of coagulation factors. In fact, the increase in fibrinolytic activity results from the effort to solve the prothrombotic state in the early phase, but results in an uncontrolled increase. Even the anticoagulant and fibrinolytic control mechanisms fail to limit the hemostatic activity to the area with tissue damage, resulting in disseminated intravascular coagulation (DIC).

Hypothesis 2

There is a command of anticoagulation mediated by the activated protein C. Whereas aPC decreases in DIC, it exponentially increases in TIC. The formation of thrombin following severe trauma and tissue hypoperfusion and the resulting thrombin-thrombomodulin complex activate protein C. Thrombin plays such a switch role in anticoagulation. Protein C ultimately mediates hyperfibrinolysis and anticoagulation though the inhibition of F5 and F8 and the inhibition of PAI. The cause of hyperfibrinolysis is the impairment of the balance between tPA and PAI-1. Persistent PAI-1 elevation was detected in patients who developed post-traumatic DIC even on the 5^{th} day.

Hypothesis 3

This hypothesis focuses on the neuro-hormonal and endothelial response stimulated by trauma. Trauma-induced tissue damage causes sympathoadrenal response and the formation of catecholamine. These catecholamines released into circulation destroy endothelial glycocalyx. Uncontrolled balancing effort to create local hemostasis provokes hypocoagulability and fibrinolysis.

Triad of Death

The main problem in trauma is the worsening of coagulation, which is already present, due to hemodilution, metabolic acidosis and hypotermia. The simultaneous presence of these three symptoms is called as the “triad of death”. Dilution may occur both physiologically and iatrogenically. In trauma-related physiological hemodilution, the increase of fluid flow into the intravascular space is directed to dilute the plasma proteins until the balance impaired with the loss of plasma due to hemorrhage is re-established. It is to say that the Starling forces reverse with the shift of fluid from the interstitium to the vascular area during the hemorrhage. Hemodilution in the resuscitation phase leads to a decrease in endogenous antifibrinolytic proteins (PAI-1, α2-antiplasmin and thrombin-activatable fibrinolysis inhibitor (TAFI)).

Finally, the administration of blood products is an

iatrogenic contribution to coagulopathy in massive hemorrhage. Transfusion of red blood cells (RBCs), plasma, and platelets in a 1:1:1 ratio results in a solution with a hematocrit of 30%, coagulation factor levels of approximately 60%, and a platelet count of 80 × 10^9/L.

Hydroxyethyl starch (HES) causes the migration of plasma proteins of blood into the interstitial space and a decrease in plasma concentration of clotting factor VIII and von Willebrand factor, and inhibits platelet function and the interaction between the activated FXIII and fibrin polymers. Platelet dysfunction is detected in 45% of trauma patients.

Metabolic Acidosis

Hypoperfusion resulting from massive blood loss is the main cause of metabolic acidosis which disrupts coagulation enzyme activity. When pH level drops from 7.4 to 7.0, the activity of FVIIa decreases by 90% and the activity of FVIa/TF reduces by more than 60% on the phospholipid surface, and therefore, the initiation phase is also impaired. In pigs, the thrombin generation decreases by 47% when the pH level lowers to 7.1 from 7.4.

Hypothermia

Body temperature of 66% of the patients is usually < 36 °C on admission. In case of hypothermia, there is a decrease in PAI 1 and alpha 2 antiplasmin. Besides aPTT prolongs in hypothermic patients.

When body temperature reaches 32 °C, VII/tissue factor complex is lowered, extending the initiation phase. However, the propagation phase remain the same and contrary to acidosis, fibrinogen synthesis decreases by 50% but its breakdown does not change. While a body temperature ranging from 33-36 °C does not lead to a major problem, the vWF-GP2b/9 interaction does not occur at < 30 °C. Nevertheless, as FFP and platelet thromboxane (TX) contain higher amount of citrate, Ca shows the highest decrease in presence of these products. However, if liver is intact and patient does not suffer from hypothermia or hypoperfusion, i.e. acidosis, citrate can be easily metabolized.

Increased levels of systemic cytokine and hormones lead to endothelial activation and the anti-thrombotic endothelium phenotype transforms into thrombotic. This process is called endogenous anti-coagulation that develops to balance this procoagulant vasculature. There are three important reasons contributing to endogenous anticoagulation all of which are associated with the status of endothelium: auto-heparinization, protein C activation and hyperfibrinolysis. In auto-heparinization, glycocalyx shedding occurs due to endothelial injury, resulting in the release of heparin-like constituents such as circulating heparin sulphate. The decreased protein C levels are replaced by the increased production of activated protein C.

The increase of fibrinolysis, the most potent endogenous anti-coagulation, takes place through the induction of early resolution of the clot by the tissue-type plasminogen activator (t-PA) is released by Weibel-Palade (WP) bodies of endothelial cells. In this context, it is thought that TDP actually corrects coagulopathy by restoring glycocalyx as well as replacing coagulation factors.

TIC also causes platelet activation and eventually thrombocytopenia via the histone complex DNA molecules in the damaged tissues. HGMB (high mobility group box protein) not only causes microvascular thrombosis, but also leads to the upregulation of TM, PAI-1 consumption and thrombin inhibition by increasing aPC.

Additionally, platelet-endothelial-leukocyte-erythrocyte-brain-derived procoagulant microparticles, P selectin, ICAM1 (intercellular adhesion molecule), syndecan 1 are also released. IL1 beta and TNF alpha elevate immediately after trauma. The increase in complex C4 b also reduces the protein S level and shows a prothrombotic effect. Damage-related molecules and cytokines, such as histone, released from all damaged cells and tissues disrupt the protein C pathway in the early phase and lead to the activation of coagulation. However, the endothelium-derived heparin-like substances also bind to antithrombine and show anticoagulant effect like heparin.

The hemostatic potential of an individual is determined by tissue damage and its location, severity of shock, inflammatory and endothelial response, genetic susceptibility and iatrogenic factors [5].

Damage control resuscitation (DCR) is a new concept in treatment of patients with massive bleeding. Permissive hypotension, hemostatic resuscitation and transfusion strategies, and damage control surgery are the components of DCR [6]. The aim is to optimize tissue oxygenation and ensure sufficient venous circulation by decreasing blood loss Another aim of the procedure is to prevent the elevation of blood pressure which may contribute to “pop the clot” through permissive hypotension. DCR involves early blood product transfusion, immediate arrest and/or temporization of ongoing hemorrhage and restoration of blood volume and physiologic/hematologic stability. Thus, it minimizes several associated side effects, including reperfusion injury, increased leukocyte adhesion and advanced acute respiratory distress syndrome, emphysema, associated acidosis and systemic inflammatory response syndrome.

Damage control surgery includes basic principles such as surgery and termination of surgical hemorrhage, placement of surgical sponges, and temporary abdominal closure when applied for critically ill patients. In the phase following the damage control surgery, the patient is immediately transferred to the intensive care unit

(ICU) for core re-warming, correction of coagulopathy and stabilization of hemodynamics.

Permissive Hypotension

All relevant guidelines in Europe recommend a target systolic blood pressure of 80-90 mmHg until major bleeding is stopped, and a systolic pressure of 100 mmHg should be maintained in patients with TBI [7,8]. Currently, anesthesiologists use liquids, blood products, and procoagulant drugs depending on the algorithms developed in line with the results of laboratory tests. In this way, there has been a significant decrease in the use of blood products. Point-of-care (POC) tests are the tests that can be performed by nurse, physician or medical laboratory technician in place of the patient, without requiring a permanent and special area, and they can lead to effective changes in patient care. These tests can give rapid results, but may be influenced by the practitioner's experience and calibration. Also, POC is an expensive method and requires training. Viscoelastic signal depends on endogenous thrombin formation, fibrin polymerization and the interaction between fibrin and glycoprotein 2b3a receptors. There is no need for a permanent and special area for performing viscoelastic tests. They are convenient to be used at the bedside. It is possible to evaluate all thrombin-mediated processes with viscoelastic tests. However, they are impacted by personal experience and calibration, and require training. In these devices, clot formation is measured using the viscoelastic signal occurring between the viscoelastic strength developing in whole blood and the pin dipped in the sample.

The interaction between endogenous thrombin formation, fibrin polymerization and fibrin and glycoprotein 2b3a receptors transforms into viscoelastic signal.

In comparison with PT and aPTT, TEG and ROTEM provide valuable information on time, speed and strength of clot formation and fibrinolysis. However, these tests are considered to be limited due to platelet dysfunction and their insensitivity to identify the point where fibrinolysis starts at low level [9].

In a review published by Tapia, et al. [10], the researchers analyzed 20 studies including a total of 12,154 patients. In conclusion Tapie, et al. [10] suggested the administration of 1:1:1 ratio of RBC:FFP:Platelet for the initial fluid resuscitation instead of 2 liters of crystalloid liquid, which was previously recommended.

The Pragmatic Randomized Optimal Platelet and Plasma.

Ratios (PROPPR) study lasted for 2 years with the participation of 12 medical centers [11]. It is the largest multi-centered prospective randomized controlled trial on trauma resuscitation to date that compared transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs. a 1:1:2 ratio in a total of 680 severely injured hemorrhagic patients. Although the results of PROPPR have some limitations, it basically supports a strategy targeting a 1:1:2 ratio.

Since tranexamic acid inhibits the formation of plasma from plasminogen, thrombin cannot be generated from prothrombin and fibrinolysis is prevented. The CRASH 2 trial spanned 274 hospitals in 40 countries involving a total of 20,211 adult trauma patients with severe clinical hemorrhage. Within 8 hours of injury, participants received a 1 g intravenous (IV) loading dose of tranexamic acid at a rate of 15-20 ml/kg over 10 minutes; a 1 g infusion over 8 hours followed. There was significant fall in mortality of the patients given tranexamic acid [12].

The European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma was first published in 2007 and updated in 2010-2013 and lastly in 2016 [13]. It is a part of the European "STOP the Bleeding" campaign. Initial intervention in trauma includes initiation of resuscitation and prevention of further bleeding, diagnosis and monitoring of bleeding, rapid bleeding control/surgical intervention, resuscitation, bleeding and coagulation management.

Conclusion

Consequently, target-oriented early coagulation management is recommended in trauma. A multidisciplinary team work should be planned. Correction of the prophylactic coagulation parameters is not recommended. The use of factor concentrates in line with the POC tests and the massive transfusion package approach serve as the basis of the treatment for traumatic coagulopathy. Nevertheless, the avoidance of hypothermia and acidosis, and the prevention of dilute coagulopathy also have an important role in reducing morbidity in trauma patients.

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