Acute Coagulopathy of Trauma-Shock

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Abstract Acute coagulopathy of trauma-shock (ACoTS) occurs in 25 % of severe trauma patients, and the mortality is fourfold higher than the patients without coagulopathy. Pathophysiology of this complex phenomenon has been emphasized in recent years. Tissue injury, tissue hypoperfusion, activated protein C and the complements play important roles in the early phase after trauma. The use of blood products, hypothermia, acidosis and inflammation are the main mechanism in late stage. Supplementation of coagulation factors and platelets is not effective. Positive resuscitation and improvement of tissue perfusion may be beneficial.

Keywords Acute coagulopathy · Trauma · Shock

Trauma is a leading cause of death in modern society. Trauma mostly occurs in young adults and has a big influence on labor force and social stability for its high mortality and disability. Thus, trauma is called "disease of developed society" [1]. Despite great progress in trauma surgery and intensive care in recent years, mortality and disability of severe trauma remains high. Recent studies showed that 25 % of patients with severe trauma developed coagulopathy in the early phase after trauma, and the mortality in those patients was fourfold higher than patients without coagulopathy [2–4].

Acute coagulopathy after trauma is gradually becoming a hotspot in clinical and laboratory research [5]. It is usually called "acute traumatic coagulopathy" [6], "early coagulopathy of trauma" [7], or "trauma-induced coagulopathy" [8]. Hess and colleagues [9] named it acute coagulopathy of trauma-shock (ACoTS) in 2008. ACoTS is

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widely accepted because it reflects the nature of the responsible underlying processes and pathophysiology of this complicated phenomenon. Here, we focus on the progress of research on ACoTS in recent years, especially on its mechanism.

1 Mechanism in the Early Stage

1.1 Tissue Injury and Hypoperfusion

Loss of clotting factors caused by bleeding and consumption in thrombosis, dilution of clotting factors for massive transfusion, and effects of acidosis and hypothermia on coagulation function are considered the main mechanism for coagulopathy in trauma patients in the early phase. This coagulation disorder is described as systemic acquired coagulopathy (SAC) [10]. Recent studies found that the exact mechanism may be not like that. Brohi and MacLeod et al. found that 25 % of patients with severe trauma developed acute traumatic coagulopathy before arriving at emergency room. These patients always did not present with acidosis and hypothermia. Acute coagulopathy could only be detected in trauma patients with tissue hypoperfusion and those with inadequate fluid resuscitation [6, 7]. This coagulopathy after trauma in early stages is also called endogenous acute coagulopathy (EAC) or ACoTS. Tissue damage and post-traumatic hypoperfusion are the necessary prerequisites for early ACoTS.

1.2 ACoTS Mediated by Activated Protein C

Further studies showed that low level of activated protein C led by tissue damage and systemic hypoperfusion in patients with traumatic shock was the main pathogenesis of early ACoTS [11]. Thrombin combined thrombomodulin (TM) on the endothelial cell surface activates protein C (APC) anticoagulation pathway. APC plays a role of anticoagulation by inactivating factor Va and VIIIa irreversibly. In vivo, endothelial protein C receptor (EPCR) could activate protein C by thrombin-TM complex, which amplified its anticoagulant effect tenfold [12].

Hyperfibrinolysis is very common after trauma due to tissue injury and shock. Protein C could develop its anticoagulant ability by activating and consumption of plasminogen activator inhibitor (PAI)-1. Which is leading to low levels of PAI-1 and the increased release of tPA from the vessel wall, and finally resulting in hyperfibrinolysis [13]. Brohi and his colleagues examined 208 trauma patients and found that coagulation was activated and thrombin generation was related to injury severity, but acidosis did not affect Factor VII or prothrombin fragments 1 + 2 levels [14].

The initial purpose of fibrinolysis may be to limit the infinite expansion of blood clots in damaged vessels. However, early clot in patients with traumatic shock

always misses its physiological role. Instead, there happens the severe imbalance of coagulation and fibrinolysis.

1.3 Platelet Dysfunction

Platelet dysfunction in the early stage after trauma remains obscure. Although the complete blood count with difference provides a platelet count, Swallow pointed that this quantitative test does not provide an assessment of platelet function [15]. Wohlauer and his colleagues reported in a study with 51 trauma patients that there were significant differences in the platelet response between trauma patients and healthy volunteers. In trauma patients, the median ADP inhibition of platelet function was 86.1 % compared with 4.2 % in healthy volunteers. The impairment of platelet function in response to arachidonic acid was 44.9 % compared with 0.5 % in volunteers [16].

1.4 Complement

Complement plays a central role in the innate immune system and is always activated in the early phase of trauma [17]. It has been reviewed that there is a significant amount of crosstalk between the complement and coagulation systems [18]. Katharina and his colleagues found that mannose-binding lectin-associated serine protease-1 (MASP-1) interacted with plasma clot formation on different levels and influenced fibrin structure. Although MASP-1-induced fibrin formation was thrombin-dependent, MASP-1 directly activated prothrombin, FXIII and TAFI. And they suggested that MASP-1, in concerted action with other complement and coagulation proteins, may play a role in fibrin clot formation [19]. On the other hand, coagulation proteases can activate the complement system. For example, thrombin, FXa, FIXa, and FXIa, can cleave the central complement components C3 and C5 into their bioactive fragments [20]. Expression of TM and activation of protein C seems to be complement-dependent in ischemia-reperfusion injury, which indicates that there may be a certain link between complement activation and ACoTS in the early stage of severe trauma.

2 Mechanism in the Late Stage

In the late phase of trauma, consumption of clotting factors, clotting factors dilution as well as acidosis, hypothermia and inflammation play more important roles in coagulopathy. At this stage, the pathogenesis of ACoTS is more similar to traditional SAC.

2.1 Use of Blood Products

In the late phase of trauma and traumatic shock, coagulopathy is caused by excessive consumption and dilution of coagulation factors due to bleeding and massive fluid resuscitation. Lack of clotting factors and platelets secondary to transfusion of blood and its components contributes to the development of ACoTS as well. Appropriate use of blood products in trauma patients can improve the coagulation function.

Fluid resuscitation for trauma shock based on blood products went through three stages: whole blood recovery before the 1970s, the strategy of blood component transfusion later, and currently the fluid resuscitation strategy based on plasma. The strategy of blood transfusion has been a controversial topic for a long time. The core problem is the ratio of FFP and RBC. Borgman and colleagues [21] found that the mortality of trauma patients who receiving massive transfusion with FFP: RBC = 1:1.4 was significantly lower than that with FFP: RBC = 1:2.5 or 1:8 group. Some scholars also believe that FFP: RBC = 1:2 can replenish clotting factors and improve the coagulation function in trauma shock [22].

2.2 Hypothermia

Hypothermia worsens coagulopathy. The most significant effect is extending the coagulation cascade, which finally leads to bleeding. Hypothermia usually accompany with dissolved dysfunction of platelet and fibrin. Gregory and colleagues reported that 57 % of trauma patients got hypothermia after trauma, and body heat loss in emergency room is more severe. Large input of cryogenic liquids is the main cause of hypothermia [23]. Frank and colleagues [24] showed that body temperature less than 33 °C produced a significant coagulopathy that was functionally equivalent to factor deficiency states, which presented when clotting factor concentration was less than 50 %. Resuscitation with cold blood and fluids creates a vicious cycle of worsening haemodilution, acidosis, hypothermia and coagulopathy.

2.3 Acidosis

Acidosis directly reduces the activity of clotting factors in both endogenous and exogenous coagulation pathway and limits the function of platelets. Note that this effect can be seen only when pH is lower than 7.2.

2.4 Inflammation

Inflammation and coagulopathy are linked through several mechanisms. More clinical findings indicate that the complement and coagulation systems are interconnected at various levels in vivo. These interactions point to alternative ways in which complement or coagulation components can potentially become activated [18]. In the late phase of trauma, low level of serum activated protein C inhibits fibrinolysis through promoting a high level of serum PAI-1, which resulting in a increase in procoagulant activity and a decrease in complement activation by reducing the plasma mannose-binding lectin and deposition of complement-3b.

3 ACoTS and Disseminated Intravascular Coagulation (DIC)

In the early phase of trauma, coagulation disorder increased bleeding, followed by a hypercoagulating state and increased the risk of thrombosis. Gando called it transformation from fibrinolytic (hemorrhagic) DIC phenotype to antifibrinolytic (thrombus) DIC phenotype. He believed that ACoTS was equivalent to DIC consumptive coagulopathy and the secondary fibrinolysis, ACoTS and non-ACoTS might be the continuous states in the process of coagulopathy [25, 26]. While Hess believed that the mechanisms in tissue trauma, shock caused by acute coagulopathy of disseminated intravascular coagulation and, trauma, inflammation caused by coagulation disorders and trauma are not the same [8]. Johansson reported one study of 80 adult trauma patients from a level 1 trauma center and found that 15 % of the patients developed ACoTS, but DIC wasn't been observed significantly [27].

The essential difference between ACoTS and DIC is a controversial issue. Authors believe that when body suffers from severe trauma, tissue injury, they will release large amounts of tissue factors, start the extrinsic coagulation pathway, and show hypercoagulating state immediately. In this case, the body reacts to promote hemostasis, reduce blood loss and maintain stable circulation, which has a protective effect on the body. But if the damage is too strong and beyond body's compensatory limit, the number and/or function abnormalities in procoagulating factors, anticoagulating factors, platelet and fibrinolytic factors will cause coagulation and fibrinolysis imbalance, ultimately lead to coagulopathy. ACoTS and posttraumatic DIC have similar pathogenesis and pathophysiology, but they are not exactly the same. However, the strict distinction between the nature of these two cannot bring a positive role to guide clinical treatment. In contrast, improving the attention of ACoTS by early detection, early diagnosis and early treatment are more important to improve the prognosis of severe traumatic patients.

4 Prevention and Treatment

Conventional coagulation tests, e.g. PT, TT, APTT, play an important role for early detection of ACoTS. However, these detections are based on one time point. They cannot reflect the continuous changes of coagulation function and the function of platelet. Thus they have little diagnostic value in fibrinolysis and are more time-consuming. Nowadays, new small viscoelastic instruments to coagulation testing get rapid progress, which promptly evaluate the clotting process and may guide blood product therapy. The Sonoclot analyzer provides information on the entire hemostasis process both in a qualitative graph and quantitative results including the activated coagulation time, clot rate, and platelet function [28]. ROTEM measures and graphically displays the time until initial fibrin formation, the kinetics of fibrin formation, clot development, and the ultimate clot strength and stability.

Thromboelastogram (TEG) is introduced in clinical practice for its wide detecting contents and intuitive results. It can reflect the dynamic process of blood coagulation, platelet function, and the full picture of blood coagulation [29]. The risk of bleeding and thrombosis cause of bleeding can be evaluated and identified, and thus guide blood transfusion and clinical management. In this way, TEG lays a solid foundation for early and rapid diagnosis of ACoTS as well as individualized treatment and even promotes the generation of early goal-directed coagulation therapy (EGCT) [30, 31].

Treatments for ACoTS include the following aspects: (1) Damage control resuscitation: Early blood transfusion, blood component transfusion, permissive hypotension and the minimum dose crystal recovery. (2) Massive blood transfusion protocol: blood transfusion $\geq$ circulating blood volume or infusion of packed red blood cells > 10 U in 24 h, or packed red blood cells > 4 U within 1 h. (3) TEG guided transfusion: design a transfusion flowchart based on TEG monitoring results. (4) Using tranexamic acid, recombinant factor VIIa.

These treatments are facing controversy. Choi and Vogel [32] noted that massive transfusion protocols have improved outcomes in adults, but limited studies in pediatrics have not shown any difference in mortality. TEG guided transfusion is widely accepted nowadays. But Hagemo and his colleges [33] reported of 184 traumatic haemorrhage patients and made a conclusion that the inter-changeability between TEG and ROTEM is limited in the trauma setting. Besides, Da and coworkers recently published a descriptive systematic review article pointed out that limited evidence from observational data suggested that TEG/ROTEM tests diagnose early trauma coagulopathy and may predict blood-product transfusion and mortality in trauma [34]. Recombinant activated factor VII (rFVIIa) is increasingly being given to treat massive bleeding. Michael studied in vitro concluded that the efficacy of rFVIIa was largely dependent on the presence of high levels of fibrinogen in reversing this severe dilutional coagulopathy [35].

The pathogenesis of ACoTS and traditional SAC is different. Supplementation of coagulation factors and platelets is not efficient. Only positive resuscitation of

shock and improvement of tissue perfusion may be beneficial. For patients with traumatic shock, active resuscitation and surgical control of bleeding are important. At the same time, we should strengthen monitoring coagulation status and make adjustments to avoid surgical wound bleeding. Based on effective, accurate and dynamic coagulation monitoring, early goal-oriented recovery can help guiding fair use of blood products, saving medical resources, and improving the prognosis of trauma patients [36].

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