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Dynamics of fibrinogen in acute phases of trauma

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Abstract

Fibrinogen is a unique precursor of fibrin and cannot be compensated for by other coagulation factors. If plasma fibrinogen concentrations are insufficient, hemostatic clots cannot be formed with the appropriate firmness. In severe trauma patients, plasma fibrinogen concentrations decrease earlier and more frequently than other coagulation factors, predicting massive bleeding and death. We review the mechanisms of plasma fibrinogen concentration decrease, which include coagulation activation-induced consumption, hyper-fibrino(geno)lysis-induced degradation, and dilution by infusion/transfusion. Understanding the mechanisms of plasma fibrinogen concentration decrease in severe trauma patients is crucial.

Keywords: Coagulopathy, Disseminated intravascular coagulation, Fibrinolysis, Massive bleeding, Transfusion, Fibrinogen, Trauma

Background

Fibrinogen is a glycopeptide that facilitates the formation of blood clots. It is synthesized in hepatocytes, with a molecular weight of 340 kDa [1, 2]. The plasma fibrinogen concentration is 1.5–4.0 g/L (as measured using the Clauss method), the highest level among other coagulation factors [1, 2]. As a unique precursor of fibrin, fibrinogen cannot be compensated for by other coagulation factors; if fibrinogen levels are insufficient in bleeding situations, fibrin clots for hemostasis cannot be formed with appropriate firmness [1, 2]. Furthermore, fibrinogen also acts as the ligand for glycoprotein IIb/IIIa receptors, found on the platelet surface, thereby accelerating platelet aggregation, similar to the role of the von Willebrand factor [2, 3]. In cases of thrombocytopenia, clot strength increases in direct proportion to plasma fibrinogen concentration, independent of platelet count [4]. Therefore, in acute phases of severe trauma, where bleeding control is important, fibrinogen plays a central role in hemostasis.

Fibrinogen level in acute phases of trauma

In cases of severe trauma, depleted plasma fibrinogen levels are frequently observed before dilution by infusion [5–9]. Furthermore, plasma fibrinogen levels deteriorate more frequently and earlier than other routine coagulation parameters (prothrombin time, activated partial thromboplastin time, and platelet count) in severe trauma patients [5]. In a Japanese multicenter retrospective study, 25% of severe trauma patients (Injury Severity Score ≥ 16) had decreased plasma fibrinogen concentrations on arrival at the emergency department [6]. Critical (≤1.0 g/L) and abnormal (1.0–1.8 g/L) fibrinogen levels were also reported in 21 and 44% of severe trauma patients who required massive transfusions, respectively [8]. Decreased plasma fibrinogen levels on arrival at the emergency department are an independent predictor of massive transfusion requirement and death in severe trauma patients [5–9].

Although decreased plasma fibrinogen levels on arrival at the emergency department are an important risk factor of poor outcomes, the plasma fibrinogen concentration threshold considered as critically low has not been well-established in trauma patients. A decade ago, guidelines suggested that plasma fibrinogen concentrations of 1.0 g/L represented the critical threshold in bleeding patients [10]. However, recent guidelines have suggested that concentrations should be maintained over 1.5–2.0 g/L in severe trauma patients [11]. Furthermore, several retrospective studies indicated that fibrinogen levels ≤1.9 g/L on emergency department admission

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were independent predictors for massive bleeding and death [6, 12]. Based on these findings, the appropriate critical plasma fibrinogen threshold will be 2.0 g/L.

Mechanisms of plasma fibrinogen decrease

Since, plasma fibrinogen concentrations decrease earlier and faster than other coagulation factors in severe trauma patients [5, 9, 13], elucidating the responsible mechanisms is of particular interest. There are three proposed mechanisms for plasma fibrinogen decrease: (1) coagulation activation-induced consumption, (2) hyper-fibrino(geno)lysis-induced degradation, and (3) dilution by infusion/transfusion. Both coagulation activation-induced consumption and hyper-fibrino(geno)lysis-induced degradation are caused by severe trauma itself (Fig. 1).

Coagulation activation-induced consumption

Following trauma, and particularly blunt trauma complicated by severe tissue injury, massively injured tissues accelerate spontaneous thrombin generation, induced by pro-coagulants in plasma (Fig. 2) [14–17]. These circulating pro-coagulants are known as damage-associated molecular patterns (DAMPs) [18–26] and microparticles [27–32] released from injured organs/tissues.

Extracellular DNA and DNA-binding proteins are the principal DAMPs that comprise the pro-coagulants detected in severe trauma patients. Histone and histone-complexed DNA fragments have been detected in the systemic circulation just after trauma [18, 19]. Furthermore, early release of high mobility group box nuclear protein 1 (HMGB-1), which is a non-histonal DNA binding protein [20–23], and mitochondrial DNA [24–26] are also observed just after trauma. Elevation of the levels of these DAMPs is related with inflammation, coagulation activation, massive bleeding, and poor outcome [18–26].

Various cell-derived microparticles have been detected during the acute phase of severe trauma [27–32]. Platelet-derived microparticles are well-known pro-coagulants in the acute phase of trauma [27–29]. Furthermore, leukocyte-, erythrocyte-, and endothelial cell-derived microparticles are also released into the systemic circulation in the acute phase of trauma (29, 30). In animal models of brain trauma, brain-derived microparticles that expressed neuronal or glial cell markers were detected in the systemic circulation [31, 32]. These microparticles were confirmed to express not only pro-coagulant phosphatidylserine but also tissue factor on their membranes [29, 31, 32].

These DAMPs and microparticles are released into the plasma from injured organs/tissues just after trauma and activate the coagulation cascade following the conversion of fibrinogen to fibrin. Furthermore, massive DAMPs and microparticles induce consumptive coagulopathy [23, 30, 31].

Hyper-fibrino(geno)lysis-induced degradation

The newly formed fibrin is subsequently converted to a D-dimer and fibrin/fibrinogen degradation products (FDP) via degradation by hyper-fibrino(geno)lysis, which is a combination of fibrinolysis and fibrinogenolysis [12, 16].

Coagulopathy caused by severe trauma is known as disseminated intravascular coagulation with fibrinolytic phenotype and is characterized by hyper-fibrino(geno)lysis, which is a combination of fibrinolysis and fibrinogenolysis

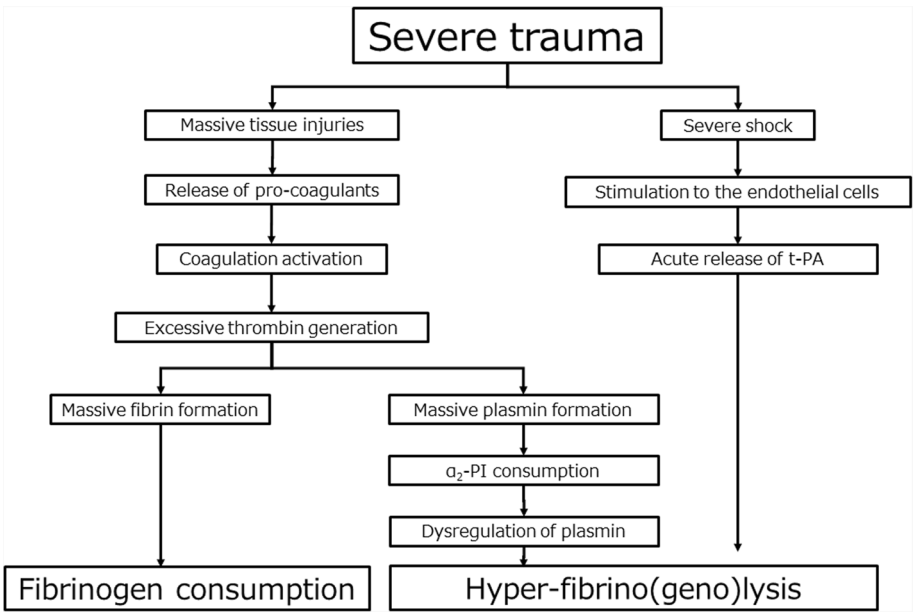

Fig. 1 Mechanisms of plasma fibrinogen concentration decrease by severe trauma itself. t-PA, tissue-plasminogen activator; α_2-PI, α_2-plasmin inhibitor

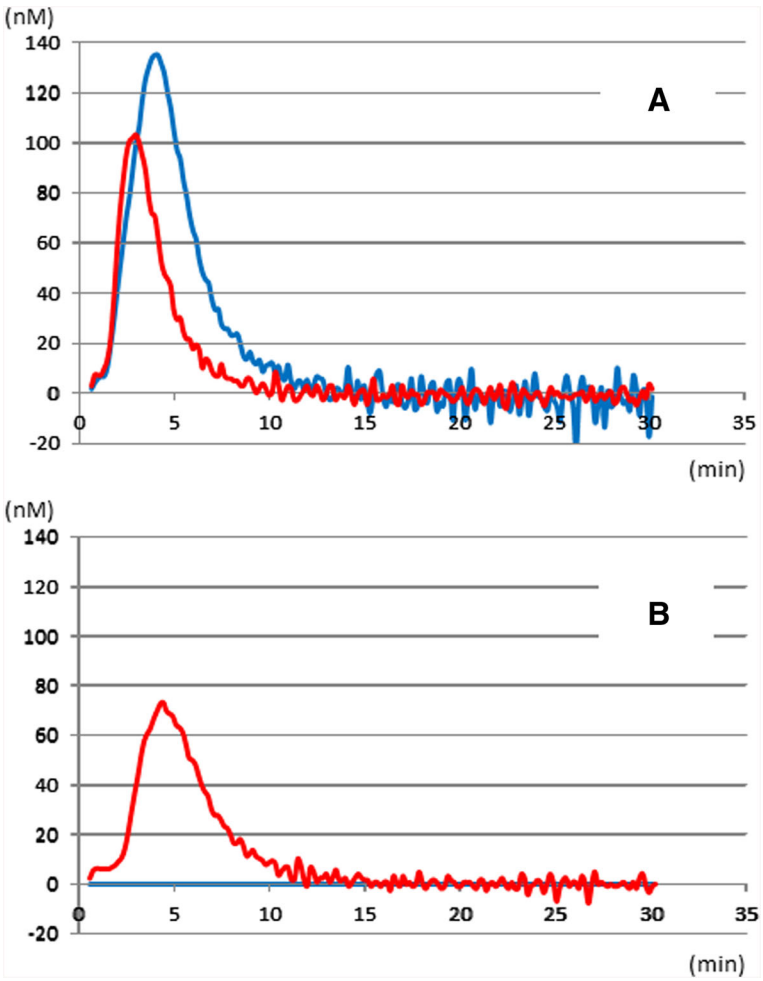

Fig. 2 Spontaneous thrombin generation in severe trauma cases. **a** Stimulated thrombin generation curve in control (*blue*) and trauma (*red*) groups. Although thrombin generation is lower in the trauma group than the control group, time to thrombin generation initiation and time to peak thrombin generation are shorter in trauma patients compared to control, suggesting coagulation activation. **b** Non-stimulated thrombin generation curve in the trauma (*red*) group. Spontaneous thrombin generation was not observed in the control group, demonstrating the presence of circulating pro-coagulants in the trauma group. This figure was adapted from [33] with permission from Wolters Kluwer Health, Inc.

[5, 12, 14–17, 33–42]. Hyper-fibrino(geno)lysis is caused by the acute release of tissue-plasminogen activator (t-PA) and by coagulation activation.

Shock-induced fibrino(geno)lysis

Weibel-Palade bodies are storage granules found in systemic vascular endothelial cells and normally contain t-PA [43–45]. The t-PA found in Weibel-Palade bodies are released into circulation during tissue hypoperfusion (severe shock), in a process known as *acute release of t-PA* [43, 44]. This rapid t-PA release from endothelial cells activates the conversion of plasminogen to plasmin and induces hyper-fibrino(geno)lysis [12, 16, 46, 47]. Shock-induced hyper-fibrino(geno)lysis are confirmed as lysis of clot formed in its test tube by thromboelastometry, such as ROTEM®, and is a predictor for massive bleeding and death [48–53]. Typical hyper-fibrino(geno)lysis detected via thromboelastometry is infrequent and is associated with very high mortality rates [48, 51, 53].

Coagulation activation-induced fibrino(geno)lysis

In severe trauma, elevations in D-dimer and FDP levels are frequently observed and are complicated with coagulopathy, regardless of severe shock [6, 12, 16, 54–59]. Although severe head trauma is not generally complicated with shock, trauma-induced coagulopathy is frequently observed with this type of injury [54, 56–58]. Kushimoto et al. [54] have indicated that patients with severe head trauma and poor outcomes have elevated fibrinogen degradation product (a kind of FDP) levels and markedly decreased fibrinogen levels on emergency department admission. Elevated fibrinogen degradation product levels correlated with elevated plasmin-α_2 plasmin inhibitor complex levels are reported to result in hyper-fibrino(geno)lysis

[54]. Many other studies reported the presence of D-dimer and FDP in not only cases of isolated head trauma [54, 56–59] but also torso trauma regardless of shock [6, 12, 16]. Furthermore, another investigation reported that hyper-fibrino(geno)lysis in severe head trauma is not directly related to shock [60]. This type of hyper-fibrino(geno)lysis is not caused by the shock-related acute release of t-PA, but by massive tissue injuries-induced coagulation activation [54, 60]. Some reports have indicated that high levels of circulating pro-coagulants are related to high levels of D-dimer and t-PA [19, 23]. In an animal study, tissue factor administration induced coagulation activation and reactive hyper-fibrino(geno)lysis without shock [55]. In severe trauma, especially blunt trauma, massively injured tissues accelerate thrombin generation [14–17]. This excessive thrombin generation not only induces fibrin formation, but also simultaneously promotes plasmin generation and the consumption of α_2-plasmin inhibitor [36, 41, 61]. Low levels of the α_2-plasmin inhibitor trigger the release of plasmin and induce hyper-fibrino(geno)lysis.

Dilution by infusion/transfusion therapy

Severe trauma-related depletion of plasma fibrinogen levels is observed before and upon emergency department admission, and levels continue to decrease after blood infusion/transfusion therapy initiation [5–9]. We showed that plasma fibrinogen levels deteriorate earlier and more frequently than other routine coagulation parameters (prothrombin time, activated partial thromboplastin time, and platelet count) in severe trauma patients after the initiation of infusion/transfusion therapies [5]. Furthermore, even in massive bleeding cases without severe tissue injuries and shock, plasma fibrinogen is more easily decreased to critical levels than other coagulation factors by infusion/transfusion therapy in the absence of plasma administration [13, 62]. Therefore, fibrinogen and/or plasma should be aggressively supplemented in patients with severe trauma [63–65].

Evaluation and treatment for fibrinogen consumption and hyper-fibrino(geno)lysis in clinical settings

In clinical settings, we usually evaluate the plasma fibrinogen level by conducting measurements in a laboratory. Although knowledge of plasma fibrinogen levels is required for prompt treatment of patients with severe trauma, the laboratory measurements of fibrinogen levels usually takes more than 30 min. Therefore, the early evaluation of fibrinogen levels is considered important [4, 7, 48, 50, 51, 53, 66]. Thromboelastometry has been widely used for early evaluation of fibrinogen level in severe trauma patients [4, 7, 48, 50, 51, 53]. However, the technique requires 10 to 15 min to measure fibrinogen levels, thus, limiting its application [4, 7, 48, 50, 51, 53]. Another technique used for early evaluation of fibrinogen levels is by measuring the levels using a compact whole blood coagulation analyzer (CG02N; A&T Corporation, Kanagawa, Japan) [66, 67]. The analyzer can rapidly measure fibrinogen concentrations in whole blood within 2 min, allowing for a rapid and accurate diagnosis of fibrinogen deficiency [66, 67]. In any case, it is important to promptly evaluate fibrinogen deficiency and to supplement fibrinogen and/or plasma in severe trauma patients [63–65].

Early evaluation of hyper-fibrino(geno)lysis is difficult in clinical settings. Shock-induced hyper-fibrino(geno)lysis is diagnosed via thromboelastometry [48–53]. However, the technique requires more than 30 min to evaluate hyper-fibrino(geno)lysis [48–53]. Furthermore, coagulation activation-induced fibrino(geno)lysis cannot be evaluated based on thromboelastometry [68]. However, note that elevated D-dimer levels are reflected not only in shock-induced hyper-fibrino(geno)lysis but also in coagulation activation-induced fibrino(geno)lysis [6, 68]. Therefore, hyper-fibrino(geno)lysis may be evaluated via evaluation of D-dimer levels in patients with acute phase trauma [6, 68]. When hyper-fibrino(geno)lysis is observed or speculated in acute phase of trauma, anti-fibrinolytic drug (tranexamic acid) should be administrated as soon as possible [69].

Conclusions

Although fibrinogen is an important factor in hemostasis, it is easily decreased to critical levels in severe trauma patients [5–9, 13, 62]. To avoid hyper-fibrino(geno)lysis, which deteriorates fibrinogen concentrations, early administration of an anti-fibrinolytic drug (e.g., tranexamic acid) improves severe trauma patients' mortality rates [69]. Aggressive supplementation of fresh frozen plasma is effective in countering decreased fibrinogen concentrations [63]. Studies evaluating effective fibrinogen supplementation in severe trauma are currently underway [70, 71].

Abbreviations

DAMPs: Damage-associated molecular patterns; FDP: Fibrin/fibrinogen degradation products; t-PA: Tissue-plasminogen activator

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