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Coagulopathy and Traumatic Brain Injury: Overview of New Diagnostic and Therapeutic Strategies

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Abstract

Coagulopathy is a common sequela of traumatic brain injury. Consumptive coagulopathy and secondary hyperfibrinolysis are associated with hypercoagulability. In addition, fibrinolytic pathways are hyperactivated as a result of vascular endothelial cell damage in the injured brain. Coagulation and fibrinolytic parameters change dynamically to reflect these pathologies. Fibrinogen is consumed and degraded after injury, with fibrinogen concentrations at their lowest 3-6 h after injury. Hypercoagulability causes increased fibrinolytic activity, and plasma levels of D-dimer increase immediately after traumatic brain injury, reaching a maximum at 3 h. Owing to disseminated intravascular coagulation in the presence of fibrinolysis, the bleeding tendency is highest within the first 3 h after injury, and often a condition called "talk and deteriorate" occurs. In neurointensive care, it is necessary to measure coagulation and fibrinolytic parameters such as fibrinogen and D-dimer routinely to predict and prevent the development of coagulopathy and its negative outcomes. Currently, the only evidence-based treatment for traumatic brain injury with coagulopathy is tranexamic acid in the subset of patients with mild-to-moderate traumatic brain injury. Coagulation and fibrinolytic parameters should be closely monitored, and treatment should be considered on a patient-by-patient basis.

Keywords: traumatic brain injury, blood coagulation disorders, fibrinolysis, fibrinogen, fibrin fibrinogen degradation products

Introduction

Traumatic brain injury (TBI) has been noted to be associated with disordered coagulation,[1-3] characterized by consumptive coagulopathy and secondary hyperfibrinolysis associated with hypercoagulability, as well as an excessively hyperactive fibrinolytic pathway induced by vascular endothelial cell damage in the injured brain. Hyperactivation of the fibrinolytic pathway leads to the exacerbation of bleeding, one of the most important sequelae of TBI.[4-6] This article reviews what is currently known regarding the incidence and mechanisms of coagulation disorders in TBI, as well as the associated recommended laboratory tests and management.

Definition and Prevalence of Coagulopathy Following TBI

The definition of coagulopathy is complex. Coagulation parameters are often used to define coagulopathy, including prothrombin time international standard ratio (PT-INR), activated partial thromboplastin time (APTT), and platelet count. Generally, a diagnosis is made with a PT-INR > 1.1-1.5, APTT > 32-60 s, and/or platelet count < 50-120 × 10^9/L.[1,7] In addition, PT > 13.0-16.0 s, PT ratio < 70%, fibrinogen concentration < 1.5-2.0 g/L, D-dimer elevation, α2-plasmin inhibitor (α2-PI) levels < 60% of normal, and disseminated intravascular coagulation (DIC) score ≥ 2-6 are used.

Coagulopathy as defined by PT, APTT, and platelet count in isolated TBI has been reported to occur in 13%-54% of patients (head Abbreviated Injury Scale [AIS] score[8]

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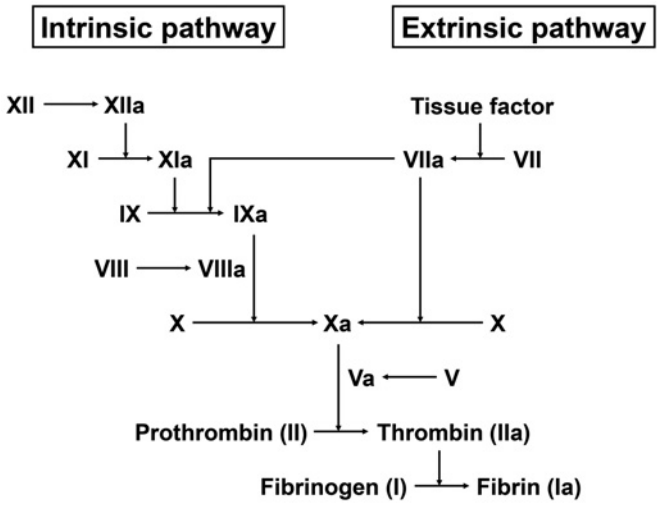

Fig. 1 The coagulation cascade is divided into the intrinsic pathway and extrinsic pathway.

> 3 and extracranial AIS score < 3).[1,7] This wide range may be due to the definition of coagulopathy, time of blood collection, or type and severity of TBI. A meta-analysis of 22 studies of patients with isolated TBI[1] showed that coagulopathy occurred in 35.2%. In addition, a large trauma registry study in Germany[3] reported that of 3,114 patients with isolated TBI, 706 (22.7%) had coagulopathy on admission.

Mechanism of TBI-induced Coagulopathy

Tissue factor (TF), which is abundant in the adventitia of cerebral arteries and astrocytes, is a major initiator of the coagulation protease cascade.[9,10] The leakage of TF into the circulation associated with direct vascular injury or TF expressed on vascular endothelial cells by endotheliopathy triggers the coagulation cascade, resulting in the formation of the TF/Factor VII/VIIa (FVII/FVIIa) complex and the activation of the extrinsic pathway (Fig. 1). The TF/FVIIa complex is responsible for converting FIX and FX into activated FIXa and FXa, forming thrombin, which, in turn, activates the cofactors FV and FVIII. The tenase complex (FVIIIa/FIXa) amplifies the coagulation cascade by activating FX into FXa. The prothrombinase complex (FVa/FXa) and thrombin constitute a common pathway that activates prothrombin to thrombin, the central proteolytic enzyme of the coagulation cascade (Fig. 1). Excessive production of thrombin systemically, as well as at the site of injury (thrombin burst), can lead to organ failure due to impaired microcirculation and to consumptive coagulopathy. Fibrinogen is converted by thrombin to insoluble fibrin, which is the major protein component of a thrombus. Fibrin binds to activated platelets and stabilizes the platelet clot produced by primary hemostasis to form a fibrin clot (secondary hemostasis).

Tissue hypoperfusion associated with trauma results in the massive release of the tissue-type plasminogen activator (t-PA) from vascular endothelial cells. Fibrin clumps are degraded by plasmin, which is produced after the activation of plasminogen by t-PA or urokinase-type plasminogen activator (u-PA). Plasmin causes cleavage of cross-linked fibrin polymers, resulting in the formation of fibrin degradation products (secondary fibrinolysis) (Fig. 2), leading to DIC with the fibrinolytic phenotype.[11] Direct degradation of fibrinogen is also observed in severe trauma, in which the fibrinolytic system is activated separately from coagulation activation and thrombus formation.[12,13] Pathological degradation of fibrinogen by plasmin produces fibrinogen degradation products (primary fibrino[geno]lysis) (Fig. 2). The measurement of fibrinogen/fibrin degradation products (FDP) has been used as a screening test for fibrinolytic activity. As this test cannot distinguish between primary and secondary fibrinolysis, however, a method was developed for measuring D-dimer, a degradation product of stabilized fibrin that reflects secondary fibrinolysis.

TBI is also thought to cause platelet dysfunction directly.[14,15] Platelet dysfunction is identified by the inhibition of the platelet-activating adenosine diphosphate (ADP) and arachidonic acid (AA) receptors.[16,17] Damage to brain tissue and vessels is thought to activate inflammatory pathways via endothelial damage, and platelet dysfunction contributes to the interaction of the coagulation and inflammatory pathways via the complement system, exacerbating coagulopathy as the activation of one amplifies the activation of the other.[18,19]

Time Course of Coagulation and Fibrinolytic Parameters in the Acute Phase of TBI

Nakae et al.[20] examined the time course of coagulation and fibrinolytic parameters, including platelet count, PT, APTT, fibrinogen levels, and D-dimer, during the acute phase of 234 isolated TBI patients on admission (within 1 h after injury) and at 3, 6, and 12 h after injury. Platelet count decreased significantly during the first 3 h after admission, whereas PT and APTT significantly increased over the same time period. Despite the changes, all three values remained mostly within the normal range. Fibrinogen concentrations decreased significantly from admission to 3 h after injury, showed no significant changes from 3 to 6 h after injury, and then increased significantly from 6 to 12 h after injury (Fig. 3). Plasma levels of D-dimer showed the most dramatic variation. On admission, 98.7% of patients had abnormally elevated D-dimer levels, which continued to increase up to 3 h after injury and then decreased significantly (Fig. 4).

Age Differences in the Time Course of Coagulation and Fibrinolytic Parameters

Coagulopathy and advanced age are well-recognized risk

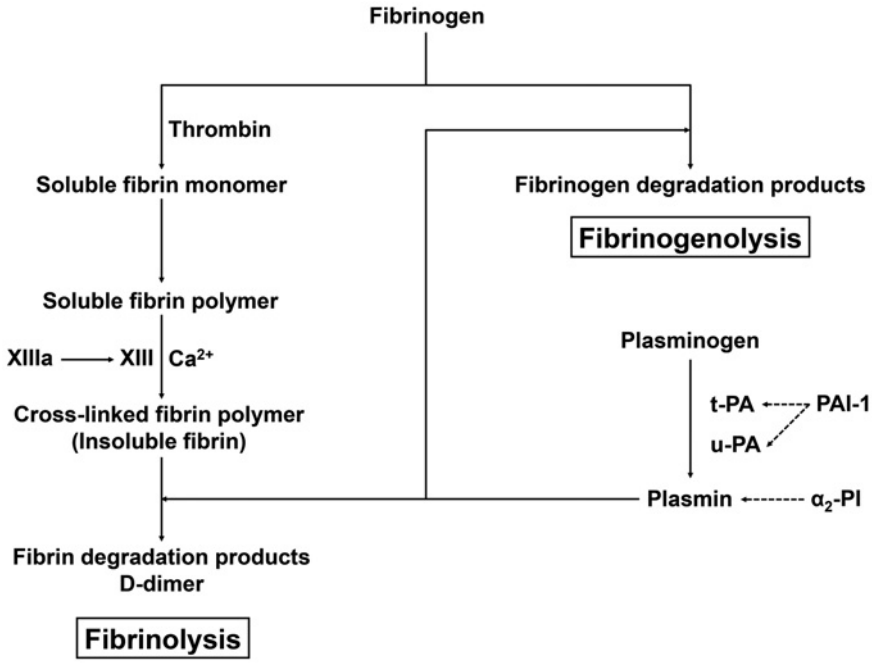

Fig. 2 The fibrinolysis cascade is divided into primary fibrinogenolysis and secondary fibrinolysis.
α_2-PI: α_2-plasmin inhibitor, PAI-1: plasminogen activator inhibitor-1, t-PA: tissue-type plasminogen activator, u-PA: urokinase-type plasminogen activator.

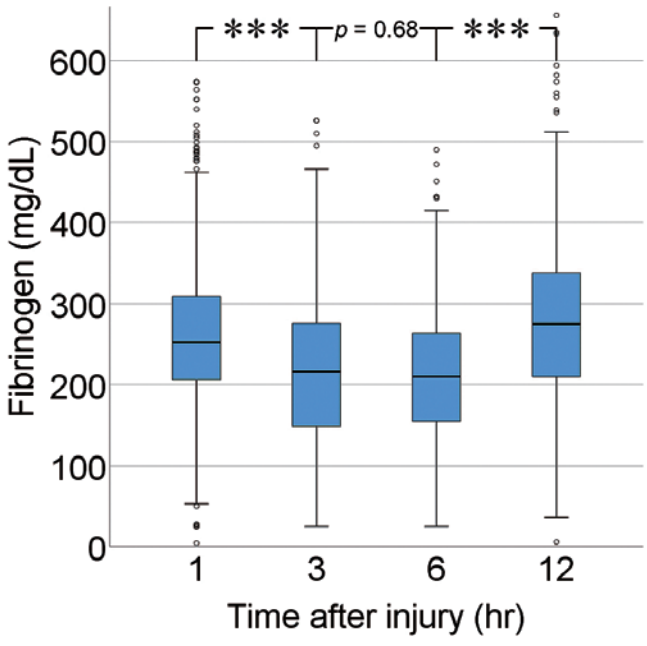

Fig. 3 Time course of plasma levels of fibrinogen on admission and at 3, 6, and 12 h after traumatic brain injury. ***$p < 0.001$. This is the original figure with a much larger number of cases based on our previous paper [Nakae R, Takayama Y, Kuwamoto K, Naoe Y, Sato H, Yokota H. Time Course of Coagulation and Fibrinolytic Parameters in Patients with Traumatic Brain Injury. *J Neurotrauma* 33: 688–695, 2016.[20]]

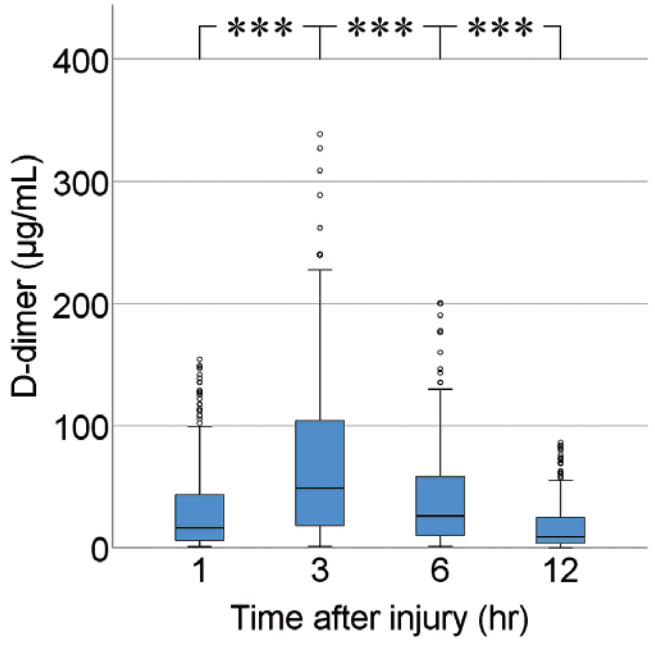

Fig. 4 Time course of plasma levels of D-dimer on admission and at 3, 6, and 12 h after traumatic brain injury. ***$p < 0.001$. This is the original figure with a much larger number of cases based on our previous paper [Nakae R, Takayama Y, Kuwamoto K, Naoe Y, Sato H, Yokota H. Time Course of Coagulation and Fibrinolytic Parameters in Patients with Traumatic Brain Injury. *J Neurotrauma* 33: 688–695, 2016.[20]]

factors for poor outcomes in TBI patients.[21] Nakae et al.[22] retrospectively evaluated TBI patients with AIS ≥ 3 in whom the plasma levels of fibrinogen and D-dimer were measured on admission (within 1 h after injury) and 3-6 h after injury. Baseline characteristics were adjusted by propensity score matching analysis, and the time course of these parameters between an elderly group (≥75 y) and a nonelderly group (16-74 y) was compared. The median fibrinogen concentration on admission was significantly higher in the elderly group than in the nonelderly group (277 mg/dL [IQR: 230-338 mg/dL] vs. 246 mg/dL [IQR: 190-314 mg/dL], $p < 0.001$). The median fibrinogen concentration decrease from admission to 3-6 h after injury was significantly greater in the elderly group than in the nonelderly group (−49 mg/dL [IQR: −96-4 mg/dL] vs. −33 mg/dL [IQR: −79-13 mg/dL], $p = 0.02$). The median plasma D-dimer admission levels were significantly higher in the elderly group than in the nonelderly group (30.7 μg/mL [IQR: 9.9-74.6 μg/mL] vs. 19.9 μg/mL [IQR: 5.7-51.8 μg/mL], $p = 0.001$). The plasma levels of D-dimer were elevated in both groups from admission to 3-6 h after injury, and the median values at 3-6 h after injury were also significantly higher in the elderly group than in the nonelderly group (81.6 μg/mL [IQR: 35.2-152.5 μg/mL] vs. 70.7 μg/mL [IQR: 32.5-134.0 μg/mL], $p = 0.04$). This suggests that the consumption and degradation of fibrinogen are greater and fibrinolysis is more severe in elderly patients than in nonelderly patients.

A pediatric study retrospectively analyzed TBI patients with AIS ≥ 3 who underwent measurement of PT, APTT, plasma levels of fibrinogen, and D-dimer on admission (within 1 h after injury) and at 3, 6, and 12 h after injury.[23] Baseline characteristics were adjusted by propensity score matching analysis, and the time course of these parameters between a pediatric (<16 y) and an adult group (≥16 y) group was compared. PT-INR and APTT at 1-12 h after injury were significantly higher, and fibrinogen concentration at 1-6 h after injury was significantly lower in the pediatric group than in the adult group; nevertheless, these parameters changed mostly within or not far off the normal range. The plasma levels of D-dimer increased in both groups at 1-12 h after injury, with no significant differences between the groups. Thus, pediatric patients show a slightly more prolonged coagulation pathway compared to adults, but a comparable increase in fibrinolysis.

Relationship between Coagulation and Fibrinolytic Parameters, Hemorrhagic Progression, and Outcome

Approximately 50% of TBI patients with coagulopathy had hemorrhagic progression of their initial cerebral contusion or intracerebral hematoma within a few hours after TBI.[24,25] Juratli et al.[24] showed in a prospective study of TBI patients that the incidence of coagulopathy was 47.1% with early hemorrhagic progression of brain contusions within the first 6 h in 43.5%. Tian et al.[25] reported in a retrospective observational study that 41.8% of TBI patients had progressive hemorrhagic injury on the second computed tomography (CT) scan, a mean of 8.8 h after the first CT scan, and that fibrinolytic parameters were elevated in these patients. Hemorrhagic extension leads to the delayed development of noncontiguous hemorrhagic lesions as well as the enlargement of the existing contusion.[5,26] Fibrinolysis is more common in elderly patients.[22] The presence of coagulopathy and expansion of intracranial hemorrhage are strongly correlated with the outcome of TBI,[1,3,27] with the mortality rates in coagulopathy defined by platelet count, PT, and/or APTT reported as 17% to 55%.[1,7]

Previous studies have reported abnormalities in various parameters such as platelet count, PT, APTT, plasma fibrinogen levels, FDP, and D-dimer as predictors of poor outcome in patients with TBI.[4,28-30] However, although coagulation and fibrinolytic parameters change dynamically during the acute phase of TBI, most studies have shown a mixture of early and delayed coagulopathy in TBI.[31] In a study by Nakae et al.[20] of isolated adult TBI patients within 1 h of injury, among coagulation and fibrinolysis parameters, a high D-dimer level was an independent risk factor for poor prognosis at all time points from admission to 12 h after injury. In addition, low fibrinogen levels on admission in elderly patients ≥ 75 y[22] and high D-dimer levels on admission in pediatric patients < 16 y[23] were shown to be independent risk factors for poor prognosis. Tian et al.[25] reported that a high D-dimer level after TBI correlates with progressive hemorrhagic injury, suggesting that hyperfibrinolysis in the acute phase of TBI contributes to poor outcome through hematoma expansion. Takahashi et al.[32] also found that fibrinolytic parameters such as D-dimer and α2-PI can be used to identify patients who "talk and deteriorate (T & D)" following admission.

Interpretation of the Time Course of Coagulation and Fibrinolytic Parameters

Prolongation of PT and APTT is attributed to TBI-induced activation of the coagulation pathway and consumption of plasma coagulation factors. The elevation of D-dimer levels is due to fibrin degradation by increased fibrinolytic activity and plasmin activity. In other words, the combination of prolonged PT and APTT and elevated D-dimer levels during the early phase of TBI can be regarded as a simultaneous progression of hypercoagulation and hyperfibrinolysis. The decrease in fibrinogen concentration up to 3 h after injury is most likely attributable to its consumption in fibrin clot formation or its degradation by fibrinolytic activation. The upward trend in fibrinogen concentration after 6 h suggests a change in hemostasis characterized by fibrinolysis shutdown. This is consistent with

the decrease in plasma D-dimer levels beginning 3 h after injury. The decrease in platelet count from the time of admission to 3 h after injury may occur as a result of consumption to form platelet-fibrin clots stabilized by crosslinking immediately after TBI. The fibrinolytic parameter D-dimer increases sharply from immediately after injury to 3 h after injury and remains elevated for at least 12 h after injury, again supporting the concept that patients presenting within 12 h of injury, and especially within 3 h of injury, are at a higher risk for bleeding due to hyperfibrinolysis.[20]

Hyperfibrinolysis can exacerbate bleeding by impairing clot formation through the breakdown of the formed fibrin clot and the consumption of coagulation factors. T & D is usually defined as a rapidly progressive disturbance of consciousness (Glasgow Coma Scale [GCS] score ≤ 8) within 2 d after injury,[33-35] but in most patients, the GCS score decreases within a few hours after injury.[36] It has been suggested that hyperfibrinolysis during the acute phase of TBI is also involved in its pathogenesis.[32]

Prevention/Management of Coagulopathy Following TBI

Treatment options for coagulopathy associated with TBI include antifibrinolytic drugs such as tranexamic acid (TXA); fibrinogen replenishment with fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrate; coagulation factor replenishment with recombinant factor VIIa (rFVIIa) or 4-factor prothrombin complex concentrate (4F-PCC); and platelet concentrates.

TXA

TXA is a synthetic derivative of the amino acid lysine that prevents fibrinolysis by inhibiting the lysine binding site of plasminogen.[37] In 2010, the Clinical Randomization of Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial,[38] a large, international, multicenter, randomized, placebo-controlled trial examining the effect of TXA on mortality and the need for blood transfusions in adult trauma patients with significant bleeding, showed that all-cause mortality was significantly lower in the TXA group than in the placebo group. However, the results suggested that there was heterogeneity depending on the timing of TXA administration and the site of trauma. The CRASH-2 trial reported that administration of TXA within 3 h of injury is effective, and after 3 h, it can cause adverse events.[38,39] A systematic review of two randomized controlled trials (RCTs),[40] including the CRASH-2 trial, showed that TXA treatment reduced the mortality of TBI patients compared with placebo. A matched cohort study of the Japanese Observational study for Coagulation and Thrombolysis in Early Trauma (J-OCTET)[41] reported that 28 d mortality of TBI patients treated with TXA within 3 h of injury was significantly lower than those not treated with TXA.

In 2019, the CRASH-3 trial,[42] a large, international, multicenter, randomized, placebo-controlled trial examining the effects of TXA on patients with TBI within 3 h of injury, was reported. The primary outcome, TBI-related mortality, did not significantly differ between the TXA and placebo groups. However, the results suggested that there was heterogeneity depending on disease severity. Patients with mild-to-moderate TBI with GCS 9-15 or with bilateral reactive pupils had lower TBI-related mortality in the TXA group than in the placebo group. In addition, a systematic review of four RCTs,[42] including the CRASH-3 trial, showed that TXA reduced TBI-related mortality. There was no difference in the incidence of adverse events between the TXA and placebo groups in any of these studies. On the basis of the findings to date, it is reasonable to administer TXA as soon as possible within 3 h of TBI.

FFP

In trauma patients with significant bleeding, fibrinogen is decreased at the earliest phase of injury.[43,44] Fibrinogen is also an important coagulation factor for clot firmness.[45,46] There is a consensus that immediate clotting factor replenishment with FFP transfusion, as well as RBC transfusion, improves outcome in patients with massive extracranial bleeding.[47,48] However, the efficacy of FFP transfusion in TBI is not certain, and many reports deny its efficacy.[49-52] In a matched cohort study of TBI patients, Zhang et al.[52] reported that the group with a poorer outcome or death received more perioperative FFP transfusions compared with the better outcome/survival group. In addition, the incidence of all complications such as acute respiratory distress syndrome and pneumonia was significantly higher in patients who received FFP transfusions than in patients who did not receive them. However, although the purpose of FFP transfusion is to replenish fibrinogen, these studies did not examine changes in fibrinogen concentration during FFP transfusion. The risk of perioperative hemorrhagic complications in nontraumatic conditions is high at fibrinogen concentrations < 150-200 mg/dL, and thus, a fibrinogen level of 150-200 mg/dL has been suggested as an indication to administer FFP, cryoprecipitate, and fibrinogen concentrate in general trauma patients.[48] In a retrospective study of patients with isolated TBI in which plasma fibrinogen concentrations were measured over time, Nakae et al.[53] reported that in the FFP transfusion group, a fibrinogen level of ≥150 mg/dL at 3 h after injury was associated with a better outcome. They also argued that FFP transfusion should be considered not only for patients with low fibrinogen levels on admission but also for patients with plasma fibrinogen levels within the normal range on admission and with high D-dimer levels as their fibrinogen levels had been found to subsequently decrease significantly. The trend of decreasing plasma fibrinogen concentration from 3-6 h after injury may represent a fibri-

nolysis shutdown, and Etemadrezaie et al.[50] suggested that FFP transfusion at >3-6 h after injury may supply coagulation factors for thrombus formation and may increase the frequency of a microvascular thrombus. This could lead to subtle cerebral ischemia that is occult on CT scans. Similarly, early transfusion of FFP to TBI patients with high fibrinogen levels may lead to hypercoagulation and cerebral ischemia. It is important for clinicians to track plasma levels of fibrinogen and D-dimer from the time of admission and calculate the timing, threshold, and volume of FFP transfusion.

Cryoprecipitate and fibrinogen concentrate

Cryoprecipitate and fibrinogen concentrate have a high fibrinogen concentration, allowing for efficient fibrinogen replenishment. Cryoprecipitate is mainly used in the United States and the United Kingdom, and fibrinogen concentrate is mainly used in Europe, except the United Kingdom. The only high-quality study[54] that showed an association between cryoprecipitate administration and reduced mortality was an observational study of war trauma patients. The other studies[44,55] did not find any association between them. For fibrinogen concentrate, a trauma registry study in Germany[56] found that 6 h mortality was lower in the fibrinogen concentrate group than in the control group, but there was no difference in the overall hospital mortality. A single-center RCT of coagulation factor concentrates, including fibrinogen concentrate and/or PCC and/or FXIII concentrate, versus FFP in severe trauma patients with coagulopathy[57] found that the rapid correction of coagulopathy with coagulation factor concentrate reduced the need for rescue therapy. However, a systematic review of 26 studies[58] found no significant difference in mortality between the fibrinogen concentrate and control groups.

There are only a few small observational studies on the administration of cryoprecipitate[59,60] or fibrinogen concentrate[61] in TBI patients, and the effects are not clear. In Japan, the correction of acquired hypofibrinogenemia by fibrinogen concentrates and cryoprecipitates has not been approved.

rFVIIa

rFVIIa was originally developed for the treatment of hemophiliacs with inhibitors and was subsequently used to treat bleeding in patients with acquired hemophilia. There have been two RCTs of rFVIIa in trauma patients requiring massive transfusion,[62,63] both of which concluded that there was no significant difference in mortality between the rFVIIa-treated group and the control group. A systematic review of 16 RCTs and 48 observational studies, including non-trauma,[64] also found no significant difference in mortality between the two groups. The European guidelines on the management of major bleeding and coagulopathy following trauma do not recommend the use of rFVIIa as first-line treatment.[48]

There is only observational study-level evidence for the effect of rFVIIa on TBI patients. In a recent matched cohort study, Lombardo et al.[65] showed that rFVIIa was not associated with reduced mortality in patients with isolated TBI. Yuan et al.[66] reported that the use of low-dose rFVIIa (20 μg/kg) was effective in correcting coagulopathy and preventing the occurrence of progressive hemorrhagic injury in patients with isolated TBI, but there was no significant difference in mortality between the rFVIIa group and the non-rFVIIa group. The use of rFVIIa for the treatment of traumatic coagulopathy is an off-label indication, and it has been suggested that administration may increase the risk of thromboembolic complications.[67]

4F-PCC

4F-PCC replenishes deficient coagulation factors in patients treated with vitamin K-dependent oral anticoagulants, including factors II, VII, IX, and X; protein C; and protein S. Emergency reversal with 4F-PCC in trauma patients taking vitamin K-dependent oral anticoagulants is recommended in the guidelines,[48] but the effect of 4F-PCC on traumatic coagulopathy is not clear, and there is only observational study-level evidence. In a matched cohort study of trauma patients, Jehan et al.[68] showed faster correction of PT-INR, lower RCC and FFP transfusion volumes, and lower mortality in a 4F-PCC plus FFP group compared with the FFP group. There was no significant difference in thromboembolic complications between the two groups. There are no reports on the efficacy of 4F-PCC in TBI patients with coagulopathy. The use of 4F-PCC for the treatment of traumatic coagulopathy is also an off-label indication.

Platelet concentrates

Platelet-concentrate transfusion for coagulopathy in TBI patients is considered in two situations: thrombocytopenia due to consumptive coagulopathy and platelet dysfunction induced by trauma. Schnüriger et al.[69] reported that a platelet count of $<175 \times 10^9$/L was significantly associated with exacerbation of traumatic intracranial hemorrhage and a platelet count of $<100 \times 10^9$/L was an independent predictor of death. It is thought to be a fact that low platelet count is associated with hematoma progression and death. However, because platelets are released from the bone marrow and spleen, platelet counts are usually within the normal range in the early phase of traumatic coagulopathy and there is controversy regarding the threshold and timing of platelet-concentrate transfusion. A small prospective trial by Briggs et al.[14] showed that platelet transfusion improved platelet dysfunction caused by aspirin, but not by trauma. There is no evidence for platelet-concentrate transfusion in patients with TBI in the anticipation of improving platelet dysfunction.

Viscoelastic devices

The viscoelastic hemostasis assay (VHA) is an alternative to standard laboratory tests that measures the viscoelasticity of blood associated with clot formation under low shear stress. It provides information on time to clot formation, clot strength, and clot lysis in a shorter period of time, and allows assessment of the different components of the coagulation and fibrinolytic cascade and their respective contributions to the kinetics. Because it can measure clot formation in whole blood, the interaction between platelets and the coagulation cascade can be evaluated. Two commercially available instruments - thromboelastography (TEG, Hemonetics, Braintree, MA, USA) and rotational thromboelastometry (ROTEM, TEM International GmbH, Munich, Germany) - are widely used. Evidence is increasing to support the use of thromboelastography and rotational thromboelastometry to reduce the need for blood transfusions and to improve outcomes in severe trauma patients. A single-center RCT[70] found that the group using thromboelastography in goal-directed massive transfusion protocols for resuscitation of severe trauma patients had a lower mortality rate and required fewer plasma and platelet transfusions in the early stages of resuscitation than the group using conventional coagulation assays. Although the European guidelines on the management of major bleeding and coagulopathy following trauma recommend the use of VHA to monitor coagulation-fibrinolysis,[48] a recent multicenter RCT[71] reported that there was no difference in overall survival between VHA-guided major hemorrhage protocols for the prevention and treatment of coagulopathy and protocols using conventional coagulation testing. A systematic review of 16 articles[72] showed that abnormal thromboelastography profiles in TBI patients were associated with poor outcome. In addition, a meta-analysis of TBI patients from the two RCTs[72] showed a significant improvement in 28-day mortality with VHA-guided management, but a quality rating of "very low" by the Grading of Recommendations Assessment, Development, and Evaluation system. Large RCTs specific to TBI are needed to confirm the benefit of VHA in TBI patients.

Current status of treatment for coagulopathy associated with TBI in Japan

The currently approved treatments for coagulopathy associated with TBI in Japan are TXA administration and FFP transfusion. Although there is heterogeneity in the effects of TXA depending on the severity of TBI, there is no evidence that TXA causes more adverse events. TXA should be administered as soon as possible within 3 h of TBI. It is also important to replenish coagulation factors by transfusing appropriate amounts of FFP while monitoring plasma levels of fibrinogen and D-dimer, as in trauma patients with heavy bleeding.

Conclusion

Coagulation and fibrinolysis undergo dynamic changes in the acute phase of TBI. Routine measurement of coagulation and fibrinolytic parameters such as fibrinogen and D-dimer is necessary to predict the development of coagulopathy and expected outcomes. Currently, the only evidence-based treatment for coagulopathy is TXA for a subset of patients, but we need to monitor coagulation-fibrinolysis parameters and consider treatment on a patient-by-patient basis.

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Conflicts of Interest Disclosure

All authors declare that there are no conflicts of interest (COIs) regarding this article according to the criteria of the Japan Neurosurgical Society. Our self-reported registration of our COI status has been submitted to the society.

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