Coagulopathy after traumatic brain injury: incidence, pathogenesis, and treatment options

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Coagulopathy after traumatic brain injury (TBI) is frequent and represents a powerful predictor related to outcome and prognosis. The complex pathophysiological mechanisms of the coagulopathy of TBI are multifactorial and remain still undefined. The nature of the coagulation abnormalities differs between severe TBI and non-TBI with somatic injuries. The current hypothesis for the development of coagulopathy after TBI includes combinations of both hypo- and hypercoagulable states promoted by the magnitude and the extent of the injury resulting in a variable degree of secondary injury via subsequent ischemic and hemorrhagic lesioning. The proposed underlying mechanisms may comprise the release of tissue factor (TF), hyperfibrinolysis, shock, and hypoperfusion thus triggering the protein C pathway, disseminated intravascular coagulation, and platelet dysfunction. Hemocoagulative disorders after TBI may be amenable to treatment, and adequate and timely management may protect from secondary injury and poor outcomes. Functional assays such as viscoelastic tests may be supportive in early detection, diagnosis, and guidance of treatment. This review summarizes the current understanding with regard to frequency, pathogenesis, diagnosis, and treatment of the coagulopathy after TBI.

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Traumatic brain injury (TBI) is often associated with hemocoagulative disorders but incidence rates vary considerably between studies (10%-90%) due to differences in study design, inconsistency in the definition for coagulopathy, diversity in the magnitude of injury, and the mix between early and delayed disturbances.[1] According to a recent meta-analysis of 34 studies reporting the frequencies of coagulopathy after civilian TBI, one out of three patients suffering from TBI displays signs of coagulopathy.[1] While hemocoagulative disorders may occur in >60% of patients with severe TBI,[2] in mild head injury coagulopathy is uncommon (<1%).[3] Wafaisade and coworkers have recently assessed retrospectively the TR-DGU (Trauma-Registry of the German Society for Trauma Surgery) database for frequency, outcome, and risk factors of acute coagulopathy in isolated TBI.[4] Out of 3114 patients, 706 (22.7%) were coagulopathic upon emergency room (ER) arrival and stepwise logistic regression analysis identified the following independent risk factors for the development of acute coagulopathy after TBI: 1) severity of head trauma as reflected by Abbreviated Injury Scale for head (AIS_{head}); 2) Glasgow Coma Scale (GCS) at scene ≤8 points; 3) hypotension ≤90 mmHg at scene or upon ER arrival; 4) prehospital intravenous fluid administration ≥2000 mL; and 5) age ≥75 years.

It has been observed that the number of patients with isolated TBI and coagulopathy may double within the first 24 hours after trauma, and that hemostatic abnormalities reflected by impaired global coagulation parameters may continue until the third day after injury or even longer.[5] Lustenberger and coworkers have reported on 127 patients with isolated severe TBI in which coagulopathy defined as thrombocytopenia and/or elevated international normalized ratio (INR) and/or prolonged activated partial thromboplastin time (aPTT) occurred at mean 23 ± 2 hours (range 0.1-108 hr [0-4.5 days]) after ER admission with a mean duration of 68 ± 7.4 hours (range 2.6-531 hr [0.1-22.1 days]).[6] In this study, the time interval to the onset of coagulopathy decreased substantially with increasing magnitude of injury. Early hemocoagulative abnormalities occurring within 12 hours after admission along with markers of devastating head injury (AIS_{head} 5),

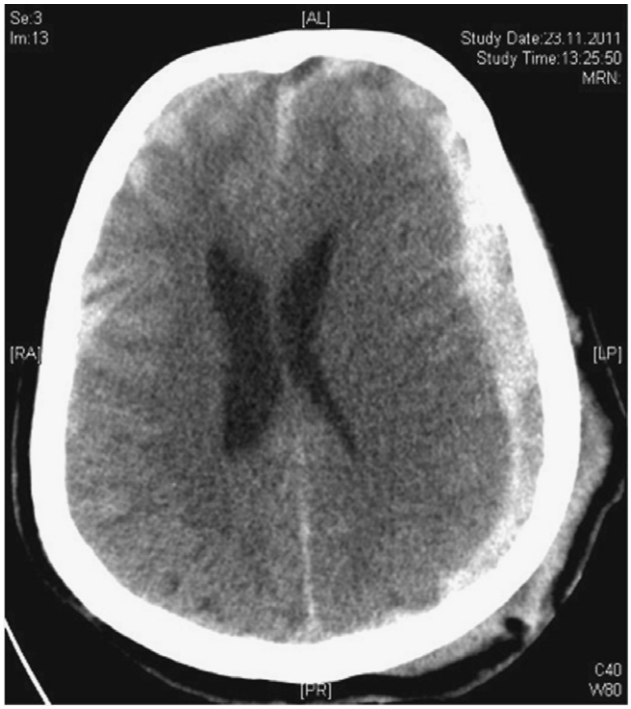

Fig. 1. Cranial computed tomography of a 70-year-old male with significant TBI showing bilateral subdural hematoma, subarachnoid hemorrhage, midline shift to the right, and brain edema. Upon arrival in the trauma bay global laboratory testings indicated severe coagulopathy with an INR 2.04, aPTT 81.1 seconds, and d-dimer >35 mg/L.

penetrating mechanism, subdural hematoma (SDH), and low GCS were independent risk factors for mortality. Those patients developing coagulopathy within 24 hours of injury had a mortality rate of 55% versus 23% in those developing abnormalities at a later stage after 24 hours.[6] Figure 1 shows a computed tomography (CT) scan of the head of a 70-year-old male with significant traumatic injury to the brain after a 3-meter fall from a garage roof resulting in combined bilateral SDH, subarachnoid hemorrhage, midline shift to the right, and massive brain edema with beginning entrapment. The global coagulation profile upon ER arrival showed an INR of 2.04, an aPTT of 81.1 seconds, and d-dimer of >35 mg/L.

COAGULOPATHY IN TBI IS A PREDICTOR FOR PROGNOSIS

Coagulopathy upon ER arrival in TBI represents a powerful predictor related to outcome and prognosis.[1,4,5] The risk of dying in patients with coagulopathy after TBI is about 10 times higher than in patients without coagulopathy, and the risk of unfavorable outcome in surviving patients is even more than 30 times higher if coagulopathy is present upon ER arrival.[1] Several authors have claimed that laboratory parameters for coagulation may be a better predictor for outcome and mortality than midline shift or pupillary reactivity,[7] and a variety of parameters have been suggested, e.g., fibrinogen degradation products (FDPs), aPTT, plasmin-α2-plasmin inhibitor complex, and/or decreased fibrinogen levels. Recently, the International Mission for Progression and Clinical Trial (IMPACT) proposed the prothrombin time (PT) as a powerful independent prognostic factor after TBI.[8] Abnormalities in mean PT, aPTT, and platelet counts upon ER arrival have been associated with the development of TBI-related but delayed injury defined by new intracranial lesions or lesion progression. Von Willebrand factor and thrombomodulin (TM) have been suggested as indicators of cerebral endothelial injury and increased TM levels to predict delayed brain lesioning.[9] In general, alterations in almost every single coagulation parameter after TBI have been associated with prognosis, but the interpretation of the predictive value of these parameters and outcome of different studies is complex as the result of heterogeneity in study design and/or size, populations assessed, and definitions of coagulopathy.[1] Moreover, peripheral hematologic studies may not entirely reflect persistent coagulopathy in the cerebral circulation.[10] However, the strong prognostic value of coagulopathy during the first 24 to 72 hours after TBI and the association between clotting abnormalities and delayed intracerebral hemorrhage warrants early and repetitive coagulation monitoring as well as adequate control of it.

PATHOGENESIS OF COAGULOPATHY IN TBI

The complex pathophysiological mechanisms behind the coagulopathy of TBI are multifactorial and remain poorly defined. In healthy individuals, coagulation and lysis are well balanced to control hemorrhage and thrombosis. TBI patients are at risk of developing abnormalities in both coagulation and lysis, and the loss of this tightly regulated equilibrium can either result in hypercoagulation with microthrombosis and ischemia or in hypocoagulation with substantial bleeding and progression of hemorrhagic lesions.[11] To date, there is no precise definition of what constitutes a coagulopathy after TBI. The likely mechanisms discussed at the moment have been summarized by Laroche and coworkers in a systematic review.[11]

Figure 2 provides an overview of laboratory tests currently available to assess coagulopathic states. Diagnostic tests and criteria for the coagulopathy of TBI are still not commonly defined but usually include a clinical condition consistent with coagulopathy, e.g., severe injury, together with thrombocytopenia, i.e., platelet counts <100.000 mm^3, and abnormal global coagulation tests, i.e., elevated INR and/or prolonged aPTT.[1,4,6-8,12] Real-time viscoelastic tests, e.g., thrombelastometry (ROTEM) or thrombelastography (TEG), allow the assessment of both

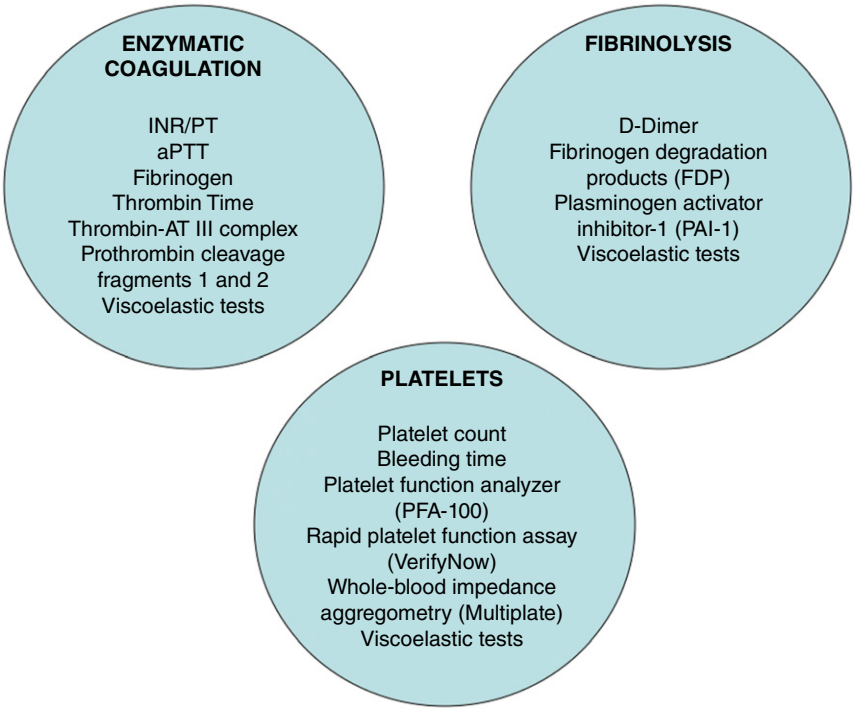

Fig. 2. Laboratory tests currently available to assess the coagulopathy after TBI (modified from[11]).

hypocoagulable and hypercoagulable states in one single test as they provide detailed information on clot formation kinetics and clot stability during dynamic clot formation.[13] These tests also provide real-time information of the effects of therapeutic interventions, e.g., blood product transfusion and/or component substitution therapy targeting the hemostasis system, and may thus be used for monitoring. Thresholds for treatment according to these viscoelastic measures as well as for all coagulation laboratory parameters are not well defined and require further study.

The nature of the coagulation abnormalities differs between TBI and non-TBI patients with multiple somatic injuries. The current hypothesis for the development of coagulopathy in TBI includes a combination of both hypo- and hypercoagulable states promoted by the magnitude and the extent of the traumatized brain tissue resulting in secondary injury via subsequent ischemic or hemorrhagic lesioning.[1,11] The potential mechanisms currently discussed are summarized in Fig. 3.

The tissue factor (TF) hypothesis

It is assumed that TBI induces massive release of TF into the systemic circulation, which results in a widespread activation of the extrinsic coagulation cascade with possible consumptive coagulopathy and a depletion of coagulation factors and platelets.[14,15] TF, the main physiological initiator of coagulation, is expressed, to a high degree, as a transmembrane protein in different cell types of the central nervous system and thus at the injury site but may also occur blood-borne contributing to the ongoing amplification of coagulation after initial injury.[16] The quantity and the temporo-spatial pattern of TF release has been associated to alterations in the blood-brain-barrier after traumatic impact, and it is suggested that this activation depends upon the amount of TF released from injured brain tissue.[17,18] Lastly, TF has been detected on circulating microparticles (MPs), shed off from either activated or apoptotic parent cells of endothelial and platelet origin, which could further trigger and promote coagulation.

The "protein C" pathway

Several studies suggest that a maladaptive protein C response to combined shock-trauma including hypoperfusion may cause 1) an immediate activated protein C (aPC)-mediated coagulopathy; and 2) a chronic protein C depletion–mediated enhanced susceptibility to infectious and thrombembolic events.[11] Shock-trauma–induced hypoperfusion promotes endothelial TM expression, which binds thrombin, thereby suppressing the generation of fibrin from fibrinogen. The thrombin–TM complex further activates protein C to aPC in the presence of calcium, which inhibits plasminogen activator inhibitor-1 (PAI-1) thus promoting hyperfibrinolysis (HF) and the coagulation factors Va and VIIIa.[19] Vice versa, the posttraumatic inflammatory response could result in a chronic depletion of protein C, causing a reduction in the inhibition of coagulation and lysis thus promotiong a hypercoagulable state. Combined hypo- and hypercoagulable states most likely triggered by the extent of the brain trauma will lead to secondary injury via ischemic and hemorrhagic lesioning.[11] Other inflammatory mediators, e.g., cytokines and complement, may also contribute to the pathogenesis of the actute coagulaopathy after TBI.

HF

Patients with TBI may be prone to develop HF, and HF has been suggested as a potential cause of bleeding diathesis after TBI. Despite its low incidence of an estimated 2.5 to 7% in all trauma/TBI patients, the presence of HF is associated with high mortality.[20] HF with fulminant clot breakdown within 30 minutes after arrival to the ER results in

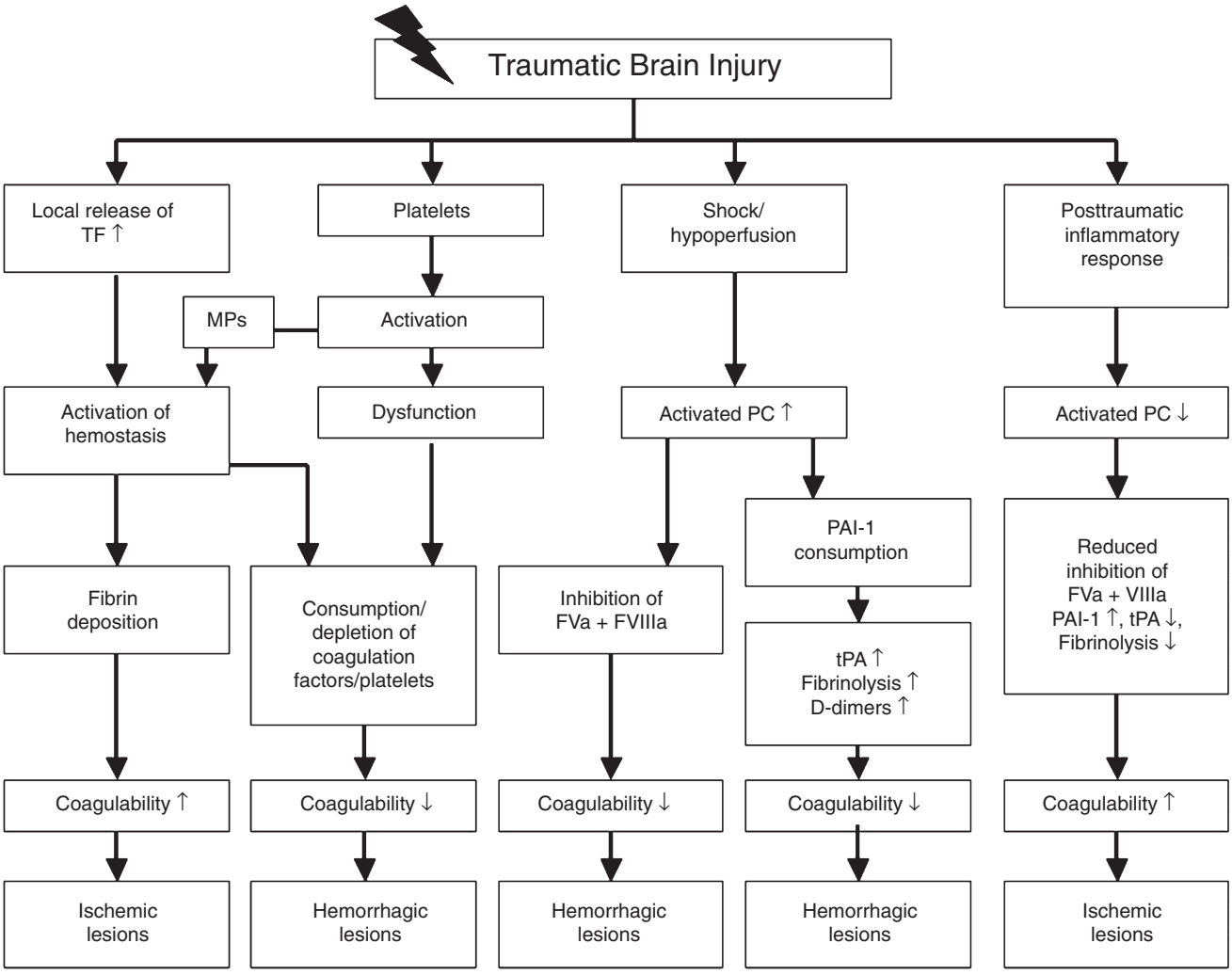

Fig. 3. Current understanding of the mechanisms underlying the coagulopathy of TBI. TBI patients may additionally suffer from hypothermia and acidosis which contribute to the further deterioration of hemostasis. FVa = coagulation factor V active; FVIIa = coagulation factor VII active; MP = microparticles; PAI-1 = plasminogen activator inhibitor 1; PC = protein C; TF = tissue factor; tPA = tissue plasminogen activator.

100% mortality, and the overall mortality of HF (88%) exceeds the mortality rate predicted by trauma and injury severity score (ISS).[21] Figure 4 displays the rapid evolvement of fulminant HF in a severely traumatized TBI patient during the prehospital phase of care until ER admission. For comparison, a reference three-channel ROTEM from a healthy volunteer is presented in Fig. 5. An estimated percent lysis of ≥15% has been suggested as a criteria for HF in viscoelastic testing.[22]

The effector of fibrinolysis is plasmin, the cleavage product of circulating plasminogen. There are two principal activators of plasminogen: 1) tissue plasminogen activator (tPA); and 2) urokinase-type plasminogen activator. While some authors have suggested an overactivation of the extrinsic pathway via TF to drive HF after TBI, others have proposed alternative mechanisms, e.g., increased levels of tPA or aPC and depletion of α–2-plasmin inhibitor resulting in an increase in plasmin.[11,19] Increased d-dimers and FDPs as well as low concentrations of α-2-plasmin inhibitor have been associated with negative outcomes after TBI, and the level of plasma d-dimer after TBI has been suggested as a predictor of progressive hemorrhagic injury/intracranial hemorrhage (PIH). Vice versa, a d-dimer level cutoff of 500 pg/μL had a 94% negative predictive value for brain injury on head CT in a pediatric cohort.[23]

The role of platelets

Decreased platelet counts and/or platelet function after TBI and thrombocytopenia early after injury have been associated with PIH and mortality.[24,25] However, the

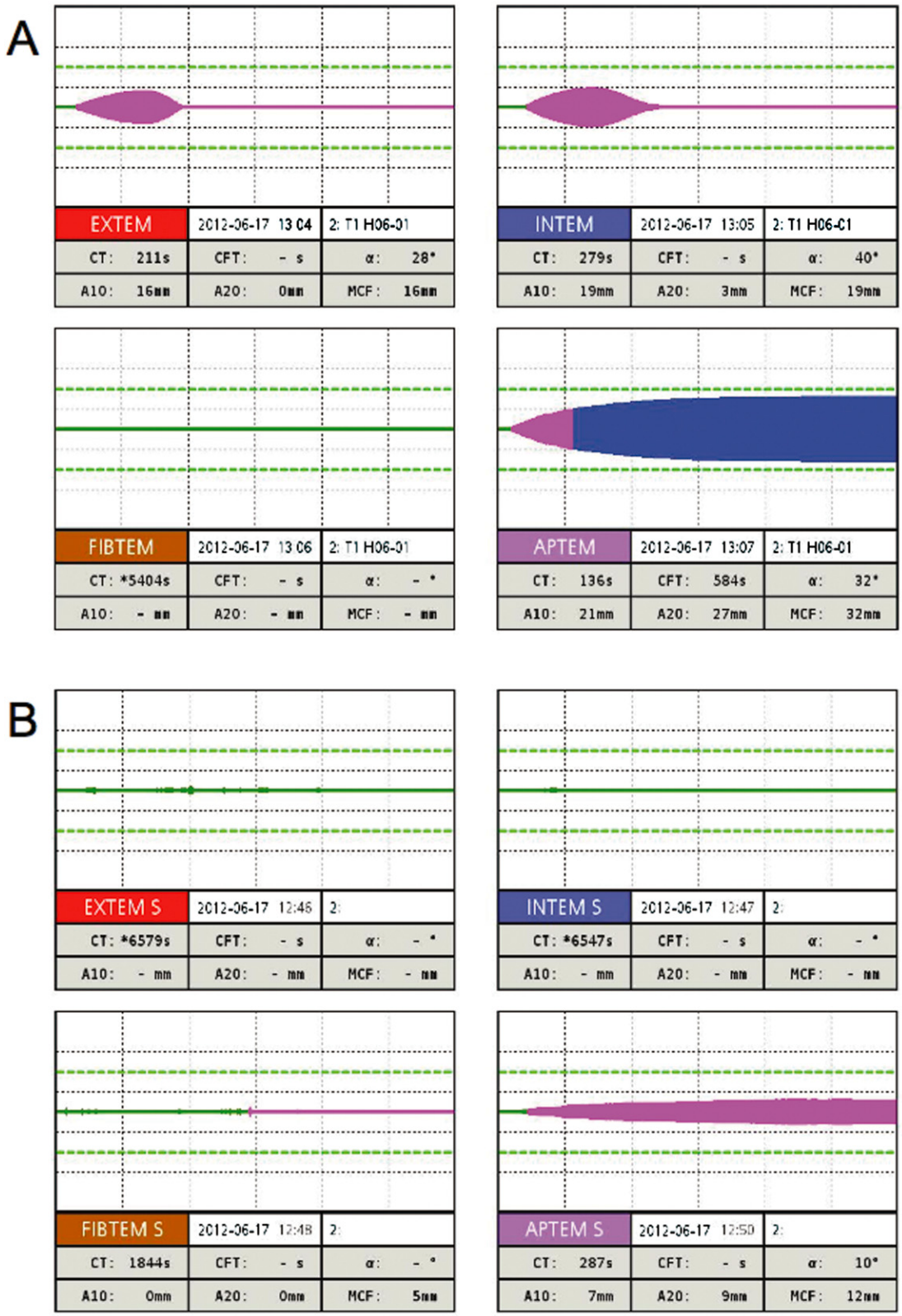

Fig. 4. Four-channel ROTEM from a trauma patient with severe TBI. Evolvement of fulminante hyperfibrinolysis (HF) during the prehospital phase of care (A) until ER admission (B). Fulminante HF in EXTEM and INTEM with no fibrin generation in FIBTEM (defibrinogenation). APTEM shows some clotting when antifibrinolytics were added to EXTEM (with permission from H. Schoechl [Salzburg/Austria]).

Fig. 5. Three-channel ROTEM from a healty volunteer for comparison (with permission from H. Schoechl [Salzburg/Austria]). EXTEM measures the activation of coagulation by thromboplastin (tissue factor) with factors VII, X, V, and I, thrombocytes, and fibrinolysis. FIBTEM records the activation as for EXTEM with the addition of the thrombocyte blocking agent cytochalasin. The resultant clot is thus formed purely by fibrin formation and fibrin polymerization; the fibrin level and the degree of fibrin polymerization can be evaluated. INTEM activates the contact phase of hemostasis, and, in the absence of heparin, this test is used as a screening test for the hemostasis system.

mechanisms for platelet dysfunction after TBI remain speculative.[11] A platelet count <100,000/mm^3 has been associated with a ninefold adjusted risk of death, and a platelet count <175,000/mm^3 has been identified as a significant predictor of traumatic intracranial hemorrhage (tICH) progression.[24] However, bleeding tendency can be present even with normal platelet count.[25] The observed platelet dysfunction in TBI patients appears to involve the cyclooxygenase pathway and means of modified thrombelastography (i.e., platelet mapping [TEG-PM]) have been shown to identify patients at high risk of bleeding complications.[25]

The role of MPs

Activated platelets, as observed after TBI, may shed off MPs after membrane phospholipid redistribution and disruption of the membrane skeleton.[26,27] The membranes of platelet-derived MPs contain receptor sites for procoagulant factors and phosphatidylserine (PS) catalyzing clotting by providing a negatively charged reaction surface with a 100-times greater procoagulant activity compared with an equal surface area on platelets. The exposure of PS facilitates binding of (activated) coagulation factors to the membranes enabling the formation of tenase-/prothrombinase-complexes. Coagulation is initiated especially in the presence of TF. Morel and coworkers have reported high levels of procoagulant MPs in the cerebrospinal fluid (CSF) and in peripheral blood at the onset of TBI.[27] The excessive release of endothelial-derived MPs mirrored the extent of the vascular damage and the sustained generation of these procagulant MPs in the CSF of a subgroup of patients correlated with poor clinical outcome.

COAGULOPATHY AND SECONDARY INJURY IN TBI

Coagulopathy plays a major role in the development of secondary injury within the further sequalae after TBI as demonstrated by the occurrence of new or progression of initial lesions on follow-up CT. In a review on 253 patients with serial CT scans after TBI the risk of developing delayed insults was 85% if at least one clotting test upon ER admission (PT, aPTT, and platelet count) was abnormal versus 31% if coagulation studies at ER admission were within reference ranges.[28] Allard and coworkers have reported intracranial hemorrhage (ICH) progression in 80% of TBI patients if any abnormal laboratory test (coagulopathic patients) was present upon admission versus 36% in noncoagulopathic patients, but all patients with abnormal partial thromboplastin time (PTT) experiencing progression.[29] ICH progression carried a fivefold higher odds of death; 32% of patients with progression died versus 8.6% without. Within their study cohort of 142 TBI patients, Oertel and coworkers have reported PIH in 48.6% of patients undergoing scanning within 2 hours of injury with initial PTT among the best predictors of PHI on logistic regression.[30] Vice versa, neuropathological studies in humans as well as in the experimental setting have demonstrated the formation of microthrombi in smaller vessels and within the microcirculation thus causing ischemia with secondary injury both locally but also at more distant sites from the injury.[31] The mechanisms behind it remain unclear but may involve both local and systemic states of hypercoagulability as well as alterations in blood flow at injury sites including stasis (see also Fig. 3).

TREATMENT OPTIONS

To date, guidelines for the treatment of coagulopathy after TBI do not exist. The opinions on preferred strategies may vary and, in principle, reflect the complexity of the problem as well as the heterogeneity in phenotype, magnitude, and temporal pattern of the disorder. In general, therapeutic strategies should focus on the primary cause, and adequate control of hemorrhage including its progression remains an important aim in the management of TBI patients. In the following the current treatment options are discussed.

Fresh frozen plasma (FFP)

The prophylactic use of FFP in TBI has recently been questioned by a randomized clinical trial in which the early empirical infusion of FFP in patients with severe head injury was associated with adverse effects, such as an increase in the frequency of delayed traumatic intracerebral hematoma and an increase in mortality (63% vs. 35%).[32] This observation is in concert with previous findings. The early administration of balanced FFP : red blood cell (RBC) ratios in patients with TBI has recently been reported in two retrospective studies but with conflicting results. In assessing data from the German TR-DGU database, Peiniger and coworkers have reported a survival benefit for high FFP : RBC ratio (FFP : RBC ratio >1:2) transfusion in blunt severe trauma patients (mean ISS 42 points) regardless of presence or absence of TBI.[33] Spinella and coworkers, however, could not reproduce this finding for the TBI population (see below).[34] The bottom line seems that FFP should only be administered in scenarios where there is actually evidence for coagulopathy. More seriously injured patients with a high risk for ongoing hemorrhage seem to benefit to a higher degree from the early administration of blood products in high ratios compared with those at lower risk, at least in the general trauma population.[35]

Platelets

The early administration of platelets in TBI is still under debate although it makes intuitive sense to do so. Spinella and coworkers have reported a survival benefit for a high platelet : RBC ratio in TBI patients while a high plasma ratio was associated with improved survival in non-TBI patients but with severe extracranial injuries.[34] Currently, platelet transfusion is utilized increasingly in TBI for the reversal of aspirin (ASA) therapy. Bachelani and coworkers have recently assessed platelet inhibition and guidance of platelet transfusion in a retrospective cohort of 84 TBI patients with ASA-induced suppression using a rapid platelet function assay, i.e., Aspirin Response Test (VerifyNow).[36] By using this approach, the authors were able to better identify patients with occult platelet dysfunction and to avoid unnecessary platelet transfusions resulting in a more adequate volume of platelets administered to correct drug-induced dysfunction. In addition, a dose–response relationship between the quantity of platelets transfused and the reversal of ASA inhibition was observed. Because the overall outcome in patients with mild TBI with ICH is favorable even when taking antiplatelet therapy before hospitalization, platelet transfusion in these patients may not be indicated.[37] A randomized prospective study on platelet administration to TBI patients on prehospital ASA medication with the primary endpoint to evaluate the effect of platelet administration on the enlargement of traumatic intracranial bleeds and clinical outcome is currently underway (see http://clinicaltrials.gov/ct2/show/NCT01135862).

Tranexamic acid (TXA): the CRASH-2 intracranial bleeding study

The recently published Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage (CRASH-2)

Intracranial Bleeding Study was the first randomized, placebo controlled trial to evaluate the effects of antifibrinolytic TXA in patients with TBI.[38] Nested into the large multicenter CRASH-2 trial, 270 patients with, or at risk of, significant extracranial bleeding within 8 hours of injury, who had also sustained a relevant TBI were randomly allocated to TXA (1 g over 10 min followed by infusion of 1 g over 8 hr; n = 133) or matching placebo (n = 137). In result, there were reported nonsignificant trends toward reduced 1) mean total hemorrhage growth on head CT measurement (5.9 mL [standard deviation (SD) 26.8] TXA vs. 8.1 mL [SD 29.2] non-TXA patients; adjusted difference –3.8 mL [95% confidence interval –11.5 to 3.9; p = 0.33]); 2) new focal cerebral ischemic lesions on head CT measurement (6 [5%] TXA vs. 12 [9%] non-TXA patients; adjusted odds ratio 0.51 [0.18-1.44; p = 0.20]); and 3) deaths (14 [11%] TXA vs. 24 [18%] non-TXA patients; adjusted odds ratio 0.47 [0.21-1.04; p = 0.06]), which justify the subsequent CRASH-3 trial (see http://crash3.lshtm.ac.uk/). The early short course of TXA was reported safe in relation to new ischemic brain lesions. TXA seems to exert its best effects when administered within the first 3 hours heavily weighted toward the first hour after injury.

Recombinant factor VIIa (rFVIIa)

The rFVIIa Traumatic ICH Study Group has recently published the results from a prospective, randomized, placebo-controlled, dose-escalation study on the safety and preliminary effectiveness of rFVIIa to limit tICH progression.[39] Patients were enrolled if they had tICH lesions of at least 2 mL on a baseline CT scan obtained within 6 hours of injury. rFVIIa or placebo was administered within 2.5 hours of baseline CT but no later than 7 hours after injury, and CT scans were repeated at 24 and 72 hours. Five escalating dose tiers were evaluated (40, 80, 120, 160, and 200 microg/kg rFVIIa). While there was no difference in mortality or number/type of adverse events observed, a nonsignificant trend for rFVIIa dose-response (80-200 microg/kg) to limit ICH volume progression was noted (rVIIa 10.1 mL vs. 21.0 mL for placebo). Asymptomatic deep vein thrombosis, detected on routinely performed ultrasound at Day 3, was observed more frequently in the combined rFVIIa treatment group (placebo, 3%; rFVIIa, 8%; not significant). In previous studies rFVIIa was able to more quickly and more economically correct INR into the operable ranges in coagulopathic TBI patients, allowing more rapid neurosurgical intervention with less blood product transfusion, and in some cases, obviated the need for surgery.[40,41] The potential significance of these results still needs to be examined in a larger prospective randomized clinical trial.

Hypertonic saline-dextran

Rhind and coworkers have recently investigated the impact of prehospital resuscitation of severe TBI patients (GCS < 8) using 7.5% hypertonic saline in combination with 6% dextran-70 (HSD) vs. 0.9% normal saline (NS) on inflammatory and coagulation cascades.[42] Hypertonic saline is an effective osmotherapeutic agent for the treatment of intracranial hypertension and has immunomodulatory properties that may confer neuroprotection. Serial blood samples from 65 patients were assessed and the results showed that plasma soluble TF and d-dimer levels were significantly lower in HSD patients, whereas soluble TM levels remained at control levels.

It remains uncertain whether specific treatment in the early hypercoagulable phase may indeed prevent lesion progression and outcome. The reversal of hypercoagulation with either antithrombin III concentrate or antiplatelet compounds is questionable or has not been tested in humans yet.

CONCLUSION

Coagulopathy after TBI is frequent and an important independent risk factor related to prognosis. The complex mechanisms underlying the development of coagulopathy after TBI remain poorly defined, and the early events must be studied in greater detail to identify the main triggers and interactions. There seems to coexist a combination of both hypo- and hypercoagulable states in TBI triggered by the extent and magnitude of the impact itself resulting in secondary injury via both hemorrhagic and ischemic lesions. The use of functional assays, e.g., viscoelastic tests, is advocated to better phenotype the coagulopathy of TBI within its temporal sequalae and to guide timely targeted therapy. Trials providing evidence-based treatment thresholds for patients with coagulopathy after severe TBI are needed.

CONFLICT OF INTEREST

The author declares that he has no conflicts of interest relevant to the manuscript submitted to **TRANSFUSION**.

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