Trauma-induced coagulopathy: What you need to know

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ABSTRACT: Trauma-induced coagulopathy (TIC) is a global inflammatory state accompanied by coagulation derangements, acidemia, and hypothermia, which occurs after traumatic injury. It occurs in approximately 25% of severely injured patients, and its incidence is directly related to injury severity. The mechanism of TIC is multifaceted; proposed contributing factors include dysregulation of activated protein C, increased tPA, systemic endothelial activation, decreased fibrinogen, clotting factor consumption, and platelet dysfunction. Effects of TIC include systemic inflammation, coagulation derangements, acidemia, and hypothermia. Trauma-induced coagulopathy may be diagnosed by conventional coagulation tests including platelet count, Clauss assay, international normalized ratio, thrombin time, prothrombin time, and activated partial thromboplastin time; viscoelastic hemostatic assays such as thrombelastography and rotational thrombelastography; or a clinical scoring system known as the Trauma Induced Coagulopathy Clinical Score. Preventing TIC begins in the prehospital phase with early hemorrhage control, blood product resuscitation, and tranexamic acid therapy. Early administration of prothrombin complex concentrate is also being studied in the prehospital environment. The mainstays of TIC treatment include hemorrhage control, blood and component transfusions, and correction of abnormalities such as hypocalcemia, acidosis, and hypothermia. (*J Trauma Acute Care Surg.* 2024;96: 179–185.

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DEFINITION

Trauma-induced coagulopathy (TIC) is a global inflammatory state accompanied by coagulation derangements, acidemia, and hypothermia, which occurs after traumatic injury.[1] The condition of TIC has long been described by other names, including "severe bleeding tendency," "defibrination syndrome," "consumptive disorder," "bloody vicious cycle," "acute traumatic coagulopathy," and more.[2] The term "trauma-induced coagulopathy" was established during the Trans-Agency Consortium for Trauma Induced Coagulopathy Workshop conducted by the National Institutes of Health in April 2010.[3] Because it encompasses a wide range of coagulation malfunctions, TIC does not have strict quantitative diagnostic criteria. However, it should be considered when coagulopathy is observed in the setting of acute trauma.

EPIDEMIOLOGY

Trauma-induced coagulopathy occurs in approximately 25% of severely injured patients.[3] There does not appear to be a difference in the incidence of TIC between sexes, but TIC may be associated with higher mortality in women than men.[4] Age does impact the incidence of TIC, with older adults being affected more frequently than younger adults and children.[3] The incidence of coagulopathy after trauma has been shown to be directly related to injury severity.[5] It has also been related to lower Glasgow Coma Scale scores, increased base excess, and lower platelet counts.[6]

MECHANISMS

The mechanism of TIC is multifaceted. Multiple models have been suggested, but the consensus is that TIC is a complex condition with numerous possible inciting events and pathways. Some proposed contributing factors include dysregulation of activated protein C, tissue-derived plasminogen activator (tPA), systemic endothelial activation, decreased fibrinogen, clotting factor consumption, and platelet dysfunction.[3,7,8] Because TIC does not have a uniform phenotype, it is expected that contributing factors may also vary between cases.[9] A graphic of proposed mechanisms of TIC is shown in Figure 1.

Activated Protein C (APC)

Protein C is a vitamin K–dependent zymogen that, when activated, is converted to a membrane-binding serine protease.[10] Protein C is activated when thrombin binds to thrombomodulin.[11] Activation of protein C is enhanced when protein C is also bound to the endothelial cell protein C receptor.[11] Once protein C dissociates from its activation complex, it then binds protein S and inactivates factors Va and VIIIa.[11] In the setting of trauma, activation of protein C may occur because of hypoperfusion.[12] Once protein C is activated, it then inhibits procoagulant activity and may lead to hypocoagulability. A prospective cohort study from Brohi et al.[13] identified that only patients with hypoperfusion, as measured by base deficit, were coagulopathic and that decreased protein C levels were associated with prolongation of partial thromboplastin times (PTT) and prothrombin times (PT). This suggests that early traumatic coagulopathy occurs alongside tissue hypoperfusion and that activation of protein C may play a role in systemic anticoagulation.[13] Furthermore, Cohen et al.[14] found that patients with severe traumatic injury showed increased activation of protein C, which was associated with coagulopathy. Elevation of activated protein C was also significantly associated with increased mortality, increased transfusion requirements, and fewer ventilator-free days.[14]

Tissue-Derived Plasminogen Activator

Fibrinolysis is primarily regulated by the plasminogen activator system, including tPA and urokinase plasminogen activator.[15] These plasminogen activators cleave circulating plasminogen to its active form of plasmin.[15] Plasmin then dissolves blood clots by cleaving cross-linked fibrin.[15] The activation of plasminogen to plasmin is inhibited by plasminogen activator inhibitor 1 (PAI-1).[15] Elevated levels of tPA and decreased levels of PAI-1 have been suggested as potential mechanisms of TIC. Cardenas

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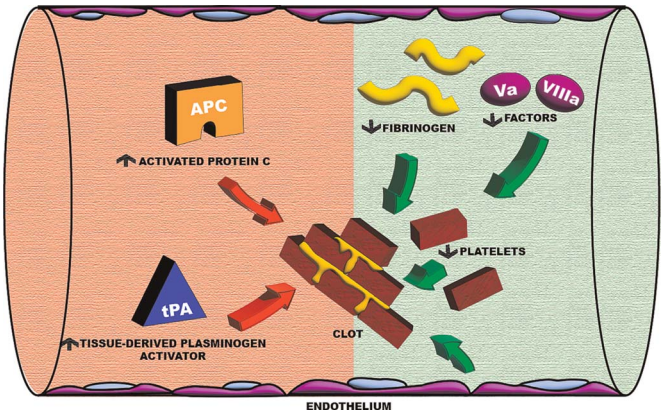

Figure 1. Proposed mechanisms of TIC include increased levels of activated protein C, increased levels of tPA, systemic endothelial activation, decreased fibrinogen, decreased clotting factor activity, and platelet dysfunction. Arrows indicate coagulant activity; red represents anticoagulant activity, and green represents procoagulant activity.

et al.[16] found that elevated levels of tPA and reduced levels of PAI-1 were associated with hyperfibrinolysis, as defined by LY30 values, among trauma patients. Chapman et al.[17] identified that depletion of PAI-1 in TIC is driven not by PAI-1 degradation but rather by an increased in tPA. The elevation of tPA following trauma has been studied and may be related to the release of tPA by microvascular endothelium in the setting of ischemic stress and signaling from vasopressin and catecholamines.[17] Johansson et al.[18] found that, among trauma patients, having elevated levels of syndecan-1, a marker of endothelial glycocalyx degradation, was associated with elevated levels of tPA and urokinase plasminogen activator. These findings suggest that hyperfibrinolysis among trauma patients may be driven by an increase in tPA, which is related to endothelial degradation, ischemic stress, and signaling by catecholamines and vasopressin.

Endothelial Activation

The endothelium may be activated through direct tissue damage and through the release of catecholamines following trauma.[19] When the subendothelium is exposed, the coagulation cascade is activated, leading to platelet activation.[20] Downstream of the coagulation cascade, fibrin is formed, which then creates a hemostatic plug with platelets.[20] The endothelium then has multiple mechanisms by which it may downregulate the coagulation cascade and maintain blood fluidity.[20] Although endothelial activation leads to upregulation of both procoagulant and anticoagulant activities, the predominant net effect is procoagulant.[7] In a prospective trial from Ganter et al.,[21] plasma levels of angiopoietin-2 were found to be associated with markers of endothelial activation, including von Willebrand factor and soluble thrombomodulin. Angiopoietin-2 was thus suggested to be a marker of endothelial activation.[21] Increased angiopoietin-2 was also associated with elevated PT, PTT, and activation of protein C, suggesting that endothelial activation was associated with coagulopathy.[21] Furthermore, a prospective cohort study from Johansson et al.[18] identified that high admission syndecan-1, a marker of endothelial degradation, was associated with increased mortality and coagulopathy.

Fibrinogen

Fibrinogen, also known as clotting factor I, is a glycoprotein primarily synthesized by hepatocytes.[22] Following vascular injury, fibrinogen participates in hemostasis both by its assistance in platelet aggregation and by its conversion to fibrin by thrombin.[22] Once formed, the fibrin clot also provides a scaffold for cell adhesion, migration, and proliferation.[22] Decreased fibrinogen has been proposed as a potential mechanism of TIC.[7] Fibrinogen has been described as the first coagulation factor to decrease following massive hemorrhage.[23] Hypofibrinogenemia is common following severe injury and has been shown to be a predictor of massive transfusion.[23] There are many proposed causes for decreased fibrinogen following major trauma, including blood loss, dilution, consumption, hyperfibrinolysis, hypothermia, and acidosis.[24] In addition, increased proteolysis after trauma can degrade both fibrinogen and fibrin, reducing their function and creating products of degradation that can alter hemostasis.[25]

Coagulation Factors

Inadequate activity of clotting factors has long been postulated as a mechanism of TIC. This may be due to a combination of hemodilution, consumption, and inactivation. Regarding hemodilution, decreased circulating levels of coagulation proteins have been identified even among healthy patients after administration of crystalloid.[26] Consumption of coagulation factors has also been reported commonly, with proposed mechanisms being compared with disseminated intravascular coagulation.[27] With regard to inactivation of coagulation proteins, aforementioned increased levels of tPA may lead to elevated levels of plasmin, which in turn is able to deactivate factors Va, VIIIa, and XIIIa.[28–30] In addition, in a case-control study out of Grady Memorial Hospital, patients with TIC had been shown to have decreased activity of common and extrinsic factors, including factors V and VII.[31] Together, these evidences suggest that activity of coagulation factors may be decreased in TIC by a variety of mechanisms.

Platelet Dysfunction

Platelets are central to the cell-based model of hemostasis.[32] After hemostasis is initiated with a damaged vessel wall, there is rapid adhesion, activation, and aggregation of platelets to the subendothelial extracellular matrix.[33] Coagulation factors then aggregate on the activated surface of platelets and begin forming a matrix of cross-linked fibrin.[33] However, it is not merely the presence or the function of platelets that matters but also the balance of platelets with coagulation factors. Imbalances in the interplay between platelets and coagulation factors have been shown to lead to increased risk of bleeding and thrombosis.[33]

EFFECTS

Inflammation

Inflammation in TIC occurs because of stimulation of the immune system after hypoxia and tissue damage activate the endothelium. The immune system components activated include aspects of both innate and adaptive immunity.[34] A multiple-trauma rat model

identified increased white blood cells, interleukins, and T-cells after significant hemorrhage.[34] A prospective cohort study of trauma patients from Johansson et al.[18] found that patients with high circulating syndecan-1 had elevated levels of catecholamines, interleukin 6, and interleukin 10 as well as evidence of coagulopathy.

Coagulation Derangements

Stages

It is suggested that TIC occurs in multiple "stages" or "phases," each with its own phenotype.[3,35]

Early TIC

Early TIC is typically characterized by hypocoagulability and generally refers to the first 6 hours after injury.[3] Degree of tissue hypoperfusion, as measured by base deficit, appears to be directly related to the degree of admission coagulopathy.[13] The presence of early coagulopathy has been shown to predict mortality in trauma.[36] A prospective cohort study from MacLeod et al.[36] found that an initial abnormal PT increased the adjusted odds of death by 35% and that an initial abnormal PTT increased the adjusted odds of death by 326%. Decreased fibrinolysis in the early phase of TIC may be protective for some patients.[37]

Late TIC

Late TIC is typically characterized by hypercoagulability.[3] The term *late* generally refers to 24 hours or later after injury.[3] The late phase of TIC is thought to be driven by the prothrombotic effects of endothelial activation and by thrombin generation.[35,38] In a prospective case-cohort study of trauma patients, Park et al.[39] identified that thrombin generation was an independent predictor of VTE after trauma. Late TIC could contribute to thrombotic events and multiorgan failure and may occur hours to days after injury.[9]

Acidemia

Acidemia in TIC occurs because of lactic acidosis from tissue damage, hypoxia, and hemodilution.[7] It is exacerbated by resuscitation with crystalloids, which are acidotic solutions with high chloride content.[40] Acidosis may decrease the activity of coagulation factors and accelerate fibrinogen consumption.[41,42]

Hypothermia

Hypothermia in TIC may occur because of heat loss and reduced heat production but also because of iatrogenic factors such as repletion with room temperature fluid or blood products and body exposure during trauma surveys.[43] Significant decreases in platelet and coagulation factor activity occur at core body temperatures below 33°C.[44]

DIAGNOSIS

Trauma-induced coagulopathy may be diagnosed by conventional coagulation tests (CCTs), viscoelastic hemostatic assays (VHAs), or a clinical scoring system. Conventional coagulation tests that may be used include platelet count, Clauss assay to measure fibrinogen level, international normalized ratio, thrombin time, PT, and activated PTT.[3,5,45] Viscoelastic hemostatic assays that may be used include thrombelastography (TEG) and rotational thrombelastography (ROTEM).[46] Viscoelastic hemostatic assays may provide results more quickly than CCTs, but their use in guiding resuscitation efforts is not necessarily associated with an improvement in survival.[47]

Conventional Coagulation Tests

In a retrospective study from Brohi et al.,[5] the presence of coagulopathy after trauma was defined as a PT of more than 18 seconds, activated PTT of more than 60 seconds, or thrombin time of more than 15 seconds (1.5 times normal). These values were taken from the British National Blood Transfusion Service and the American College of Pathologists' guidelines for coagulopathy.[5] An abnormal PTT may be more specific for predicting outcomes than PT.[36] However, these measurements may take up to 60 minutes to result, and they only assess up to the first 60 seconds of clot formation. They fail to assess the quality or strength of clots, as well. In addition, while a platelet count could provide information about the number of platelets present, it does not assess platelet function.

Viscoelastic Hemostatic Assays

Thrombelastography and ROTEM are both VHAs that have been used to diagnose TIC. They are both point-of-care assays that allow measurement of clot formation and dissolution in real time.[48] Thrombelastography is widely available in trauma centers in North America, while ROTEM is primarily used in Europe.[49] Unlike CCTs in which blood is first spun down and plasma is isolated before running the assay, TEG and ROTEM

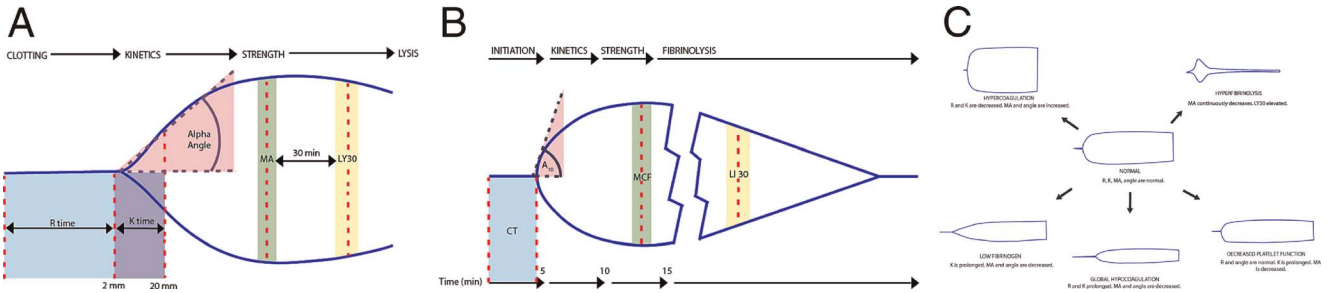

Figure 2. Viscoelastic hemostatic assay interpretation guidelines. (*A*) Example TEG curve and measurements. Reaction time represents the time it takes from initiation of the test until the curve reaches 2 mm.[52] Kinetic time represents the time it takes for the curve to extend from 2 mm to 20 mm. *α* Angle represents the angle of the slope between R time and K time. Maximum amplitude represents the greatest diameter of the curve in mm. LY30 represents the clot lysis at 30 minutes after MA. (*B*) Example ROTEM curve and measurements. Computed tomography is akin to TEG R time, A10 is akin to AA, MCF is akin to MA, and LI30 is akin to LY30.[52] (*C*) Normal TEG curve compared with curves with coagulation derangements. AA, *α* angle; A10, amplitude at 10 minutes; K time, kinetic time; LI30, Lysis Index 30; LY30, clot lysis at 30 minutes; MA, maximum amplitude; MCF, maximum clot firmness; R time, reaction time.

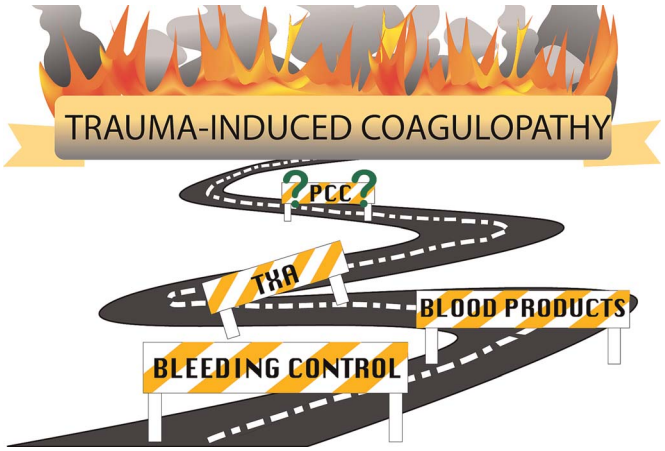

Figure 3. Roadblocks to TIC. Essential steps in the prevention of TIC include early hemorrhage control, blood product resuscitation, and TXA therapy. Early administration of PCC is also being studied. PCC, prothrombin complex concentrate.

are run using whole blood.[48,50] In TEG, a whole blood sample is manually pipetted into a cylindrical rotating cup containing a stationary pin on a torsion wire.[48] An electromagnetic transducer measures pin transduction as a clot forms and dissolves.[48] As for ROTEM, a whole blood sample is automatically pipetted into a cylindrical stationary cup containing a rotating pin.[48] An optical detector measures impedance of pin rotation, which provides information about clot formation and dissolution.[48] Key aspects of coagulation measured by TEG and ROTEM that are not assessed by CCTs include clot strength and fibrinolysis.[51] Viscoelastic hemostatic assay interpretation guidelines are shown in Figure 2.

Clinical Scoring System

The Trauma Induced Coagulopathy Clinical Score is a clinically derived numeric scoring system designed to be used by prehospital providers to identify patients in need of damage-control resuscitation.[53] Components of the score include general severity of injury (rated at either 0 for "noncritical" or 2 for "critical"), blood pressure (rated at 5 if any systolic blood pressure measures less than 90 mm Hg or 0 if the systolic blood pressure is always higher than 90 mm Hg), and extent of significant injuries (1 point each for significant injuries to the head/neck, left upper extremity, right upper extremity, left lower extremity, or right lower extremity and 2 points each for significant injuries to the torso, abdomen, or pelvis) for a total possible score of 18.[53]

PREVENTION

Preventing TIC begins in the prehospital phase with early hemorrhage control, blood product resuscitation, and tranexamic acid (TXA) therapy.[54] Early bleeding control may involve wound compression and packing, tourniquet application, pelvic binder placement, and tamponade, depending on the anatomic location of the injury.[54] Torso hemorrhage control in the field remains problematic and rapid transportation to the trauma center is paramount.[54] Because administration of large volumes of crystalloid may lead to dilutional coagulopathy, fibrinolysis, and poor outcomes, permissive hypotension may be maintained until blood products are available.[54,55] Many prehospital services have begun transfusing plasma, RBCs, and whole blood to reverse coagulopathies early.[56,57] If the patient is in shock, a 2-g bolus of TXA may be administered intravenously.[58] Administration of thawed plasma in the field has been associated with improved survival.[59] Prothrombin complex concentrates are being studied in randomized trials in the field and early after hospital arrival.[60,61] A schema of TIC prevention guidelines is shown in Figure 3.

TREATMENT

Because there are multiple proposed pathways that lead to TIC, there are also multiple treatments. The mainstays of treatment include hemorrhage control, blood and component transfusions, and correction of abnormalities such as hypocalcemia, acidosis, and hypothermia.[56] Hemorrhage control should be early and aggressive and may include measures such as tourniquets, direct pressure, hemostatic dressings, and retrograde endovascular balloon occlusion of the aorta.[62] Regarding blood and component transfusions, damage-control resuscitation with a massive transfusion protocol in a 1:1:1 ratio of RBCs, plasma, and platelets—or whole blood, if available—remains the criterion standard treatment.[47,63,64] Early administration of TXA (within 1 hour of injury) is also recommended to reduce exsanguination and to reduce mortality.[65] The Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (ITACTIC) trial found that there was no difference in overall outcomes between VHA- and CCT-augmented major hemorrhage protocols.[47] However, other studies have found improved survival and less blood product utilization when TEG was used to guide transfusions compared with conventional coagulation assays.[66] The American Society for Clinical Laboratory Science does not recommend using VHAs to guide trauma transfusions without an established, institutional treatment algorithm in place.[67] If VHAs will be used to guide resuscitation, other adjuncts that may be used depending on VHA results include fibrinogen concentrate, prothrombin complex concentrate, protamine, and factor XIII.[49] A TIC treatment schema is shown in Figure 4.

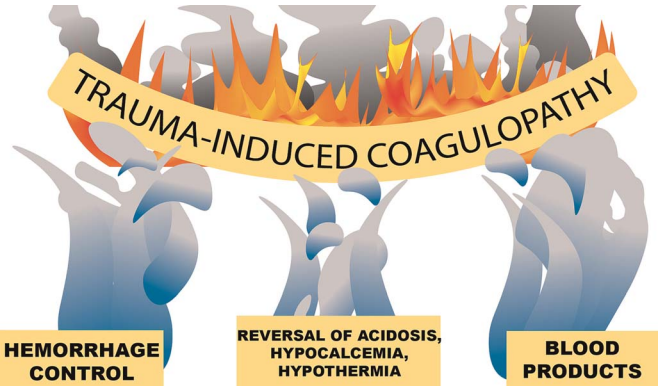

Figure 4. Putting out the TIC fire. Essential steps in the treatment of TIC include hemorrhage control, blood product and component transfusions, and correction of abnormalities such as acidosis, hypocalcemia, and hypothermia.

AUTHORSHIP

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DISCLOSURE

Conflict of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D315).

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