Trauma-induced coagulopathy: Mechanisms and clinical management

Vui Kian Ho¹*FANZCA*, Jolin Wong¹*FANZCA*, Angelly Martinez²*FCICM*, James Winearls²*FCICM*

ABSTRACT

Introduction: Trauma-induced coagulopathy (TIC) is a form of coagulopathy unique to trauma patients and is associated with increased mortality. The complexity and incomplete understanding of TIC have resulted in controversies regarding optimum management. This review aims to summarise the pathophysiology of TIC and appraise established and emerging advances in the management of TIC.

Methods: This narrative review is based on a literature search (MEDLINE database) completed in October 2020. Search terms used were “trauma induced coagulopathy”, “coagulopathy of trauma”, “trauma induced coagulopathy pathophysiology”, “massive transfusion trauma induced coagulopathy”, “viscoelastic assay trauma induced coagulopathy”, “goal directed trauma induced coagulopathy and “fibrinogen trauma induced coagulopathy”.

Results: TIC is not a uniform phenotype but a spectrum ranging from thrombotic to bleeding phenotypes. Evidence for the management of TIC with tranexamic acid, massive transfusion protocols, viscoelastic haemostatic assays (VHAs), and coagulation factor and fibrinogen concentrates were evaluated. Although most trauma centres utilise fixed-ratio massive transfusion protocols, the “ideal” transfusion ratio of blood to blood products is still debated. While more centres are using VHAs to guide blood product replacement, there is no agreed VHA-based transfusion strategy. The use of VHA to quantify the functional contributions of individual components of coagulation may permit targeted treatment of TIC but remains controversial.

Conclusion: A greater understanding of TIC, advances in point-of-care coagulation testing, and availability of coagulation factors and fibrinogen concentrates allows clinicians to employ a more goal-directed approach. Still, hospitals need to tailor their approaches according to available resources, provide training and establish local guidelines.

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INTRODUCTION

Globally, trauma accounts for the highest number of mortalities in adolescents and young adults up to 49 years old.¹ Of these deaths, a large percentage is attributable to exsanguination.² Trauma-induced coagulopathy (TIC) occurs in 25–35% of hospitalised severe trauma patients and is associated with increased incidence of bleeding, blood transfusion, multiorgan failure and death.³

The main feature seen in TIC is reduction in clot strength, or absent clot formation. This arises from endothelial dysfunction, platelet dysfunction, hypofibrinogenemia

or dysfibrinogenemia and hyperfibrinolysis, and is exacerbated by acidosis, hypothermia, haemodilution and factor consumption related to massive blood loss and large volumes of fluid resuscitation (Fig. 1).^{4,5}

However, TIC is more appropriately renamed “coagulopathic response to trauma” because the coagulopathy is not a uniform phenotype, with a thrombotic phenotype at one end and a bleeding phenotype at the other, with a series of mixed thrombotic-bleeding phenotype along the spectrum.³ Both thrombotic and bleeding phenotypes are associated with increased mortality.

¹ Surgical Intensive Care, Division of Anaesthesiology, Singapore General Hospital, Singapore

² Intensive Care Medicine, Gold Coast University Hospital, Queensland, Australia

Correspondence: Dr Vui Kian Ho, Surgical Intensive Care, Division of Anaesthesiology, Singapore General Hospital, Outram Road, Singapore 169608.
Email: ho.vui.kian@singhealth.com.sg

CLINICAL IMPACT

What is New

- This review summarises the latest understanding of the complex pathophysiology of trauma-induced coagulopathy (TIC) and appraises established and emerging advances in the management of TIC.

Clinical Implications

- TIC is a spectrum of phenotypes ranging from thrombotic to bleeding phenotypes. There is no single protocol that universally addresses TIC.
- Viscoelastic haemostatic assays can quantify the functional contributions of individual components of coagulation and permit targeted treatment of TIC but remains controversial.
- Better understanding of TIC, advances in point-of-care coagulation testing, and availability of coagulation factors and fibrinogen concentrates allow clinicians to employ a more goal-directed approach.

This narrative review is based on a literature search (MEDLINE database) completed in October 2020. Search terms used were “trauma induced coagulopathy”, “coagulopathy of trauma”, “trauma induced coagulopathy pathophysiology”, “massive transfusion trauma induced coagulopathy”, “viscoelastic assay trauma induced coagulopathy”, “goal directed trauma induced coagulopathy” and “fibrinogen trauma induced coagulopathy”. We aim to summarise the recent science on the pathophysiology of TIC and appraise both established and emerging advances in management, like goal- and diagnostic-directed therapy, as well as factor and fibrinogen concentrates.

Pathophysiology of TIC

Several mechanisms have been proposed to explain the development of TIC. The hyperfibrinolysis and coagulopathy seen in TIC are chiefly due to the effects on the endothelium related to shock, hypoperfusion and direct tissue injury.⁶ The concept of tissue injury as the driving force behind TIC is seen in that coagulopathy is present even before fluid resuscitation or massive transfusion, and correlates with severity of trauma.^{7,8}

Hyperfibrinolysis

Endothelial thrombomodulin expression is upregulated in response to tissue hypoperfusion, and together with thrombin generated by tissue trauma, forms

thrombomodulin–thrombin complex that accelerates protein C activation. Activated protein C causes coagulopathy by inactivating factors Va and VIIIa, and produces fibrinolysis by inactivating plasminogen activator inhibitor 1 (PAI-1).^{6,9} A study by Chapman et al. demonstrated that endothelial tissue plasminogen activator (tPA) overexpression is necessary for hyperfibrinolysis to occur because tPA forms a covalent complex with PAI-1.¹⁰ A functional assay for PAI-1 reserve was devised using thromboelastography (TEG) with exogenous tPA challenge. Chapman et al. concluded that because severe hypoperfusion activates endothelial cells to release tPA from Weibel–Palade bodies into the systemic circulation, the excess tPA sequesters PAI-1 into the inactive complex, thereby decreasing PAI-1 activity.

Fibrinolysis shutdown

On the opposite end of the fibrinolysis phenotype are patients who demonstrate fibrinolysis shutdown, which is associated with impaired tPA release following trauma.³ Fibrinolysis shutdown is a common phenotype and is associated with higher mortality than in patients with physiologic fibrinolysis.

This was demonstrated in a prospective study by Moore et al., who categorised patients with severe trauma based on fibrinolysis characteristics: fibrinolysis shutdown (clot lysis at 30 minutes after maximum clot strength [LY30]<0.8%), physiologic lysis (LY30 0.8–3%) and hyperfibrinolysis (LY30>3%).¹¹ There were no significant differences in baseline characteristics, including injury patterns or severity scores. Of the 32 patients with physiologic lysis, 3% died. Mortality rate increased to 17% for patients with fibrinolysis shutdown (n=33) and was 44% in patients with hyperfibrinolysis (n=115). Notably, deaths in patients with hyperfibrinolysis were mainly from massive haemorrhage, whereas deaths in patients with fibrinolysis shutdown occurred later from multiorgan failure, postulated to be from fibrin deposits in the microcirculation. Gall et al. similarly characterised 3 fibrinolysis phenotypes in 914 patients based on maximum lysis (ML) rates from rotational thromboelastometry: hyperfibrinolysis (ML>15%), physiologic fibrinolysis (ML 5–15%) and fibrinolysis shutdown (ML<5%).¹² The mortality pattern was similar to that described by Moore et al.

Endothelial factors

The endothelial glycocalyx, and its effects on the neurohormonal axis, is involved in the development of TIC. The rise in systemic catecholamine levels following trauma and haemorrhagic shock exacerbates

Fig. 1. Pathophysiology of trauma-induced coagulopathy and its detection by thromboelastometry. (Modified from Winearls J, et al. Targeted coagulation management in severe trauma: the controversies and the evidence. *Anesth Analg* 2016;123:910-24, with permission from Wolters Kluwer Health, Inc.)

A5EX: amplitude 5 minutes after coagulation time in EXTEM; A5FIB: amplitude 5 minutes after coagulation time in FIBTEM; ADP: adenosine diphosphate; AUC: area under the curve in impedance aggregometry (in thromboelastometry platelet); CT: coagulation time; CTEX: coagulation time in EXTEM; CTHEP: coagulation time in HEPTM; CTIN: coagulation time in INTEM; ML: maximum lysis (within 1 hour run time); PAI-1: plasminogen activator inhibitor-1; Thrombin Gen.: thrombin generation; TRAP: thrombin receptor-activating peptide

endothelial glycocalyx degradation, which can be associated with auto-heparinisation and increased mortality.¹³⁻¹⁵ Animal studies done demonstrated glycocalyx restoration following resuscitation with plasma, suggesting a different mechanism than merely replacement of coagulation factors.¹⁴ This effect of endothelial repair was similar in a 4-factor prothrombin complex concentrate, but was not observed following resuscitation with crystalloids or albumin.¹⁶

Platelet and fibrinogen dysfunction

The cell-based model of haemostasis recognises the role of platelets and fibrinogen in the stages of coagulation.¹⁷ In trauma, however, there remains limited understanding of the pathogenesis of platelet and fibrinogen dysfunction. Platelet levels in early trauma are usually not inordinately depressed to the point that coagulation is compromised. Despite this, evidence has shown that platelet transfusion improves haemostasis

in trauma. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) and the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) studies illustrate that rates of exsanguination may be reduced if platelet transfusions are initiated in the early stages (within 24 hours) following severe trauma.^{18,19} Furthermore, the latter suggested that a 1:1:1 ratio of plasma, platelets and red blood cells was superior to a 1:1:2 ratio in achieving haemostasis, with no increase in complications.¹⁹ This raises a possibility that platelet dysfunction, rather than a reduced platelet count, contributes to TIC. Several studies have investigated platelet aggregation after trauma and found poorer outcomes in instances of platelet dysfunction.^{20,21} Platelet dysfunction may also be associated with increased sensitivity to exogenous fibrinolytic stimuli and thereby enhanced hyperfibrinolysis.²² Meizoso et al. showed that platelet transfusion in the first week was associated with a dose-

dependent risk of persistent fibrinolysis shutdown.²³ Platelets contain large quantities of PAI-1 and α_2 antiplasmin and Vulliamy et al.'s study suggests that platelet transfusion decreases fibrinolysis due to high PAI-1 levels.²⁴

Fibrinogen levels may be decreased as early as the point of admission and low fibrinogen levels are associated with poorer outcomes including higher mortality.²⁵⁻²⁷

While the exact pathophysiology is still poorly understood, the literature is clear: TIC is associated with increased mortality.^{28,29} As more evidence emerges, the management of TIC will also likely change with our understanding.³⁰ For example, it may be possible to tailor treatment based on the identification of a patient's phenotype through viscoelastic haemostatic assays (VHAs) or other biomarkers.³

Management of TIC

The management of TIC has evolved with increased knowledge and advances in diagnostics and therapeutics, and involves addressing the many factors in the pathophysiology of TIC.³¹ This section will explore the management options, starting with more established and cruder methods and progressing to more goal-directed and diagnostic-guided approaches.

Tranexamic acid

The CRASH-2 trial was a landmark study, which demonstrated that the use of tranexamic acid in adult trauma was associated with a reduction in all-cause mortality compared with placebo.³² Subsequent exploratory analysis showed that the delayed use of tranexamic acid beyond 3 hours was associated with increased risk of death due to bleeding, thus supporting early administration.³³ However, tranexamic acid has been associated with increased rates of venous thromboembolism.³⁴ Since the publication of the study, the use of tranexamic acid has been debated extensively and the evidence remains controversial.³⁵ Nevertheless, its benefit has been corroborated in other studies,³⁶ and international guidelines have recommended its use within the first 3 hours following trauma.³¹

Massive transfusion protocols

Massive transfusion protocols represent a balanced resuscitative strategy for the rapid delivery of large volumes of blood products in a predefined ratio in the treatment of haemorrhagic shock.³⁷ There is no single correct strategy, and as such individual institutions differ widely in the trigger threshold for initiation of the massive transfusion protocols as well as the predefined ratios of blood products.³⁸ Despite these institutional

and geographical variations, it remains evident that massive transfusion protocols reduce mortality.³⁹

The PROMMTT study demonstrated improved 24-hour survival with transfusions of higher ratios of plasma and platelets at an early stage in resuscitation.¹⁸ The 2015 multicentre PROPPR trial found no difference in the 24-hour or 30-day mortality between a 1:1:1 ratio versus a 1:1:2 ratio of plasma to platelets to RBCs transfused.¹⁹ However, the group that received a 1:1:1 ratio was more likely to achieve haemostasis and less likely to die from exsanguination.

Although conventionally, a fixed ratio of blood product transfusion has been recommended, there has been increasing use of coagulation factor concentrates as an alternative to fresh frozen plasma (FFP) in the correction of trauma-induced coagulopathy. A significant concern with the use of large volumes of blood products is the potential for transfusion-associated circulatory overload and transfusion-related acute lung injury.⁴⁰

Goal-directed transfusion

Our limited understanding of the mechanisms of TIC suggests that there is no one-size-fits-all approach for massive transfusion protocols in predetermined, fixed ratios in all patients. The heterogenous nature of trauma necessitates treatment that is targeted to the individual patient's needs. In contrast to a universal transfusion protocol, a targeted approach to each patient theoretically guides individualised therapy. Goal-directed therapy is a Grade 1B recommendation in the recent European guidelines and can be achieved using standard laboratory tests (SLT) or point-of-care assays.³¹ A single-centre randomised controlled trial compared severe trauma patients who were administered a transfusion protocol guided by laboratory results with those administered a fixed-ratio transfusion protocol.⁴¹ This study showed reduced plasma wastage with a goal-directed protocol and reduced 28-day mortality in the intention-to-treat analysis. Two other studies showed that a change in protocol incorporating goal-directed transfusion was associated with a reduction in the use of blood products, a trend to mortality reduction and reduced healthcare costs.^{42,43} However, these were single-centre studies and were underpowered with small sample sizes.

The Strategy of Transfusion in Trauma (STATA) trial compared a fixed ratio protocol (1:1:1) to a TEG-guided administration of coagulation factor concentrates and fibrinogen in patients with major trauma. While the study has not been published, the interim analysis showed no difference in mortality.⁴⁴

Viscoelastic haemostatic assays

Conventional coagulation studies (prothrombin time and activated partial thromboplastin time) test isolated portions of the coagulation cascade in a laboratory, and may not be indicative of true clotting *in vivo*. There is also no functional measure of clot strength or fibrinolysis in a conventional coagulation test. Furthermore, the need to perform such tests in a centralised laboratory implies an inevitable delay in obtaining results necessary to make decisions on further blood product transfusion. VHAs, on the other hand, examine clotting dynamics in whole blood and reveal the interactions between the cellular and plasma components of blood up to fibrinolysis. The use of VHAs allows the examination of different stages in the coagulation cascade, with specific information on the initiation of haemostasis, clotting kinetics, clot strength and clot stability (or lysis).⁴⁵ Finally, VHAs are available as point of care tests with almost real-time feedback to the managing clinician.

There are two main systems available for VHAs: the thromboelastogram (TEG Hemostasis Analyzer System) (Haemonetics, Boston, US) and rotational thromboelastometry (ROTEM) (TEM Innovations GmbH, Munich, Germany). A systematic review suggested that VHAs diagnose early trauma coagulopathy and may predict transfusion and mortality.⁴⁶

TEG has been found to be a better predictor of the need for transfusion of individual blood product components compared with SLTs (prothrombin time, activated partial thromboplastin time, platelets and fibrinogen).⁴⁷ A prospective randomised controlled trial comparing goal-directed TEG-based transfusion with SLT-based transfusion showed that mortality in the VHA group was significantly reduced (19.6% vs 36.4%).⁴⁸ Both groups used a similar number of RBC units, but the SLT group used more plasma and platelet units in the early phase of resuscitation. However, this was a single-centre study and patients were randomised by weekly alternation of treatment arms. Moreover, 8 of 55 patients randomised to SLT crossed over to the VHA protocol at the request of treating physicians, which could introduce bias from non-adherence.

The Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (iTACTIC) multicentre randomised controlled trial compared the use of VHA-guided with SLT-guided transfusion in 396 adult trauma patients with haemorrhagic shock that activated the local massive haemorrhage protocol.⁴⁹ Patients were block randomised per centre and followed up until discharge or day 28. There was no difference in the primary endpoint, which was the proportion of subjects alive and free of massive transfusion (less than

10 units of RBCs) at 24 hours. There were also no differences in secondary outcomes such as the rate of organ failure, total hospital and intensive care length-of-stay, healthcare resources needed, and mortality.

Despite a lack of high-quality evidence, the use of VHAs has been advocated during massive transfusion in various trauma centres and recommended in trauma management guidelines.^{31,50,52} An example of a hospital VHA-guided transfusion algorithm is shown in Fig. 2.

A hybrid approach has also been proposed that involves the initial use of ratio-driven massive blood transfusion, followed by goal-directed therapy at a later stage.^{53–55} This hybrid approach is supported by the European guidelines, which recommend that the initial management of bleeding and coagulopathy consist of antifibrinolytic agents, coagulation monitoring and support, and notably, initial coagulation resuscitation

Fig. 2. Gold Coast University Hospital ROTEM trauma algorithm. (Reproduced with permission from Gold Coast University Hospital.)

A5: amplitude 5 minutes after coagulation time; A10: amplitude 10 minutes after coagulation time; BW: body weight; CFT: clot formation time; CRYO: cryoprecipitate; CT: coagulation time; FFP: fresh frozen plasma; FIB CONC: fibrinogen concentrate; MCF: maximum clot firmness; ML: maximum lysis; PCC: prothrombin complex concentrate; ROTEM: thromboelastometry; TXA: tranexamic acid

with FFP in a FFP:RBC ratio of at least 1:2, or fibrinogen concentrate and RBC. This is followed by further goal-directed coagulation management, in which FFP, coagulation factor concentrates, fibrinogen supplementation, platelets and calcium are replaced with goal-directed therapy guided by SLT or VHA.³¹

Coagulation factor concentrates

The use of coagulation factor concentrates as first-line therapy enables faster correction and reduces the volume of blood products transfused with a potential for fewer side effects from plasma administration.⁵⁶ A nationwide retrospective study examined outcomes of severely injured trauma patients receiving both 4-factor prothrombin complex concentrate and FFP compared with FFP alone, utilising the American College of Surgeons Trauma Quality Improvement Program database.⁵⁷ Patients were matched into 2 groups of 234 each. Using propensity-matched analysis, 4-factor prothrombin complex concentrate together with FFP was associated with decreased packed RBC and FFP requirements, lower mortality (17.5% vs 27.7%, $P=0.01$) and decreased rates of acute respiratory distress syndrome and acute kidney injury. Further randomised controlled trials are needed to better evaluate the role of prothrombin complex concentrate in major trauma.

Fibrinogen concentrate

The early use of fibrinogen concentrate was explored in the fibrinogen in the initial resuscitation of severe trauma (FiiRST) trial.⁵⁸ This randomised, placebo-controlled feasibility study of 50 hypotensive trauma patients showed increased plasma fibrinogen levels in the fibrinogen concentrate group, with 96% of subjects receiving the intervention within 1 hour. In the blinded, randomised, placebo-controlled trial of early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT-1)⁵⁹ involving adult trauma patients at 5 major trauma centres who required activation of major haemorrhage protocol, subjects were to receive either 6g of fibrinogen or placebo within 45 minutes of admission. However, only less than 70% of subjects received the study intervention in the stipulated time, suggesting that this protocol is not feasible in practice.

The Reversal of Trauma Induced Coagulopathy (RETIC) trial was a single-centre, open-label, randomised trial in Austria that compared the use of FFP with fibrinogen concentrate.⁶⁰ The study included adult patients with major trauma who had coagulopathy identified using rotational thromboelastometry. It was terminated early because of the harmful effect of

massive transfusion in the plasma arm. The primary endpoint of multiorgan failure was found to be increased in the plasma arm, although this was not statistically significant owing to the early termination of the study. The targeted use of fibrinogen concentrates was associated with earlier correction of coagulopathy, reduced transfusion of blood products and decreased rate of massive transfusion.

Platelet function analysers

The use of antiplatelet medication is common internationally and poses a bleeding risk in the setting of trauma. Point-of-care platelet function tests identify the presence of platelet dysfunction⁶¹ and have the potential to guide blood product transfusion. The 2019 European guidelines have suggested the use of point-of-care platelet function devices as an adjunct to SLT or VHA in patients with suspected platelet dysfunction.³¹ A single-centre study compared the use of TEG platelet mapping with impedance aggregometry in 52 patients in a level 1 trauma population.⁶² Results revealed weak correlation in the adenosine diphosphate channel and a moderate correlation in the arachidonic acid channel. TEG platelet mapping predicted blood product transfusion and correlated with increased base deficit, while impedance aggregometry was more predictive of mortality. The utility and validity of platelet function analysers are still evolving.

Upcoming studies of interest

We look forward to the currently recruiting Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage (PATCH) Study, a multicentre, randomised, double-blinded, placebo-controlled trial, which is investigating whether extending tranexamic acid administration to the prehospital setting for severely injured patients at risk of TIC will improve mortality and functional recovery at 6 months.⁶³ This could push the established practice of early tranexamic acid administration even earlier.

While the early use of fibrinogen concentrate has theoretical value, the E-FIT 1 trial showed issues with protocol implementation.⁵⁹ We therefore await the publication of the Fibrinogen Early in Severe Trauma (FEISTY) study.⁶⁴ This is a multicentre, randomised controlled trial comparing the use of rotational thromboelastometry-guided fibrinogen concentrate to cryoprecipitate for fibrinogen replacement in adults with traumatic haemorrhage.

Finally, early fibrinogen supplementation with high-dose cryoprecipitate, within 3 hours of injury, in adult

patients with severe trauma and major haemorrhage is being studied in the ongoing CRYOSTAT-2 trial.⁶⁵ It is a multicentre, randomised controlled trial aiming to recruit over 1,500 patients and will compare the intervention with standard therapy on 28-day all-cause mortality. This trial was done following the successful CRYOSTAT-1 feasibility study,⁶⁶ in which 86% of patients received cryoprecipitate within 90 minutes of admission.

With increasing recognition that the higher proportion of plasma found in most massive transfusion protocols may be harmful to patients, these upcoming studies that explore the use and timing of fibrinogen concentrate and cryoprecipitate will inform us if they provide better outcomes compared with the plasma-heavy approach to transfusion.

CONCLUSION

A greater understanding of TIC, coupled with advances in point-of-care coagulation testing and availability of coagulation factors and fibrinogen concentrates, allows the clinician to employ a more goal-directed approach to massive transfusion, as opposed to traditional fixed-ratio approaches. However, to achieve best outcomes, hospitals need to tailor their approaches according to available resources, provide adequate training and establish local guidelines or algorithms.³¹ Ultimately, no matter the approach, the patient will be best cared for by a highly skilled team of trauma surgeons, anaesthetists and critical care physicians trained in damage control resuscitation and surgery.

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