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Review Article

Bad blood: A coagulopathy associated with trauma and massive transfusion review

Tawnya Vernon, Madison Morgan, and Chet Morrison

Trauma Services, Penn Medicine Lancaster General Health, Lancaster, Pennsylvania

Coagulopathy in trauma patients is a known contributor to death due to hemorrhage. In fact, it seen as frequently as 35% of the time. The complexity of the coagulopathy pathway requires a deliberate and planned approach. The methods used to assess and detect if a patient is coagulopathic remain challenging, but tools have been developed to assist the practitioner to effectively manage and even quickly reverse the coagulopathy. The purpose of this review is to educate trauma and emergency medicine staff on the currently available diagnostic tools to assess coagulopathy, to provide an overview of the coagulopathy pathway, as well as provide examples of how to intervene and treat coagulopathy, including the use of crew resource management during mass transfusion protocol activations.

Key words: Fibrinolysis, fresh frozen plasma, massive transfusion protocol, packed red blood cells, platelets, trauma-induced coagulopathy, viscoelastic assay

INTRODUCTION

COAGULOPATHY IS SEEN in 25–35% of trauma patients and is a common contributor to hemorrhagic death; in fact, it is thought to be responsible for half of the hemorrhagic deaths in trauma patients who receive mass transfusions.[1–3] Upwards of 30% of trauma-related deaths are directly associated with massive blood loss, of which 10% are preventable. Coagulopathy also results in higher transfusion requirements which, in turn, significantly increases morbidity as well as mortality compared to non-coagulopathic trauma patients.[1] Mortality rates are elevated in the first hours following arrival at the trauma center in patients with uncontrolled hemorrhage due to the so-called "lethal triad", coagulopathy, acidosis, and hypothermia,[4] which reinforce each other in a vicious cycle. The majority of trauma patients become coagulopathic within 2 h, with the more severe trauma patients showing signs of coagulopathy sooner and having increased rates of mortality.[5–7] Early diagnosis of coagulopathy is thus necessary as well as quick activation of the massive transfusion protocol (MTP). The hope is that death can sometimes be pre-empted by interrupting this lethal triad before the cycle becomes irreversible. It is notable that most deaths associated with MTP to treat coagulopathy occur within the first 6 h of trauma.[4,7–10] Another group has found a fourfold increase in mortality when coagulopathy is present.[11]

Due to trauma-induced hemorrhage being the leading preventable cause of death worldwide,[10,12] Trauma-induced coagulopathy (TIC) is targeted by delivering fresh frozen plasma (FFP), platelets, and other high-dose blood components as early as possible.[12] Massive transfusion protocols are specifically crafted so that delivery of high numbers of blood products can be done in a standard fashion, and a ratio of 1:1:1 of packed red blood cells (PRBC), platelets and FFP, which most closely represents whole blood, can be given, especially as whole blood is not widely available. There has also been a recent increase of physician/laboratory-driven resuscitation to MTP because it reduces time to first transfusion, addressing coagulopathy faster, which reduces mortality.[4] It is likely that aggressive use of FFP and platelets in MTP significantly reduces 24-h mortality.[13] This review provides a summary of the relevant pathophysiological pathways, available diagnostic tools, and current interventions.

METHODS

A SYSTEMATIC REVIEW of published reports between 2003 and 2018 regarding coagulopathy associated with trauma and mass transfusions was carried out.

Corresponding: Chet Morrison, MD, FACS, FCCM, Trauma Services, Penn Medicine Lancaster General Health, 555 N. Duke St., Lancaster, PA. E-mail: cmorrison2@lghealth.org.
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Key words for this article search included: MTP, coagulopathy, trauma, trauma-induced coagulopathy, FFP, packed red blood cells (PRBC), platelets, resuscitation, thromboelastography (TEG), TEG-guided resuscitation, viscoelastic assay, traumatic hemorrhage, rotational thromboelastography (ROTEM), tissue plasminogen activator (tPA), fibrinogen, coagulation factors, and fibrinolysis. Articles were then selected that were felt to be complete and relevant to the topic of TIC. All transfusion protocols at Penn Medicine Lancaster General Hospital (Lancaster, PA, USA) were reviewed in conjunction with the articles.

Pathophysiology

A thorough understanding of the underlying pathophysiology of platelet formation and the clotting cascade is important for successful treatment and management of patients who endure severe trauma. Formation of the platelet plug is the initial response to hemostatic injury and takes place in four stages. First, platelets, activated by collagen and thrombin, adhere to the source of injury. Second, the activation subsequently leads to conformational changes on the platelet surface, causing aggregation. Third, platelets secrete alpha and dense granules. The alpha granules release fibrinogen. Finally, procoagulant activity assembles complexes in the clotting cascade on the platelet surface, depicting an interrelationship between activation of the platelet and the clotting cascade.[14] Platelets have a central role in hemostasis after injury and have been found to be inversely correlated with early mortality and transfusion (Figs 1 and 2).[15]

The clotting cascade contains both an intrinsic and extrinsic pathway. The intrinsic pathway is initiated by exposure of blood to a negatively charged surface, whereas the extrinsic pathway is activated by a tissue factor. This tissue factor interacts with activated factor VII and is the primary physiologic event that initiates clotting. Both pathways then converge to activate factor X which, when activated, converts prothrombin to thrombin. From here, thrombin converts fibrinogen into an insoluble fibrin clot.[14]

Trauma-induced coagulopathy is driven both by acute traumatic coagulopathy (ATC) and resuscitation-associated coagulopathy.[1] Acute traumatic coagulopathy is due to dysregulation of the thrombomodulin–protein C system and is directly related to injury, trauma, and shock. It presents as increased coagulation activation, coagulation impairment, and increased fibrinolysis. Increased fibrinolysis is the most prominent feature of ATC.[1] In fibrinolysis, tPA and the precursor plasminogen bind to fibrin, leading tPA to activate and turn plasminogen into plasmin. Plasmin then cuts the fibrin and rapidly degrades the clot.[16] Hyperfibrinolysis is often seen in trauma patients, and historically is a 60–100% predictor of mortality in trauma patients.[17,18] Mortality is directly associated with degree of fibrinolysis.[19] Consumption of clotting factors in the actively bleeding patient is also a significant and obvious contributor to TIC.[20,21] Resuscitation-associated coagulopathy, which includes anemia, hypothermia, metabolic acidosis, and dilution-associated coagulopathy, is secondary to the trauma and can also be a result of medical intervention. Unfortunately, these multiple aspects of TIC often reinforce each other, increasing the difficulty of hemorrhage control.

Trauma-associated coagulopathy can also be thought of as occurring in three phases. The first phase is when ATC begins by the immediate activation of hemostatic pathways. This increases fibrinolysis and coagulation along with

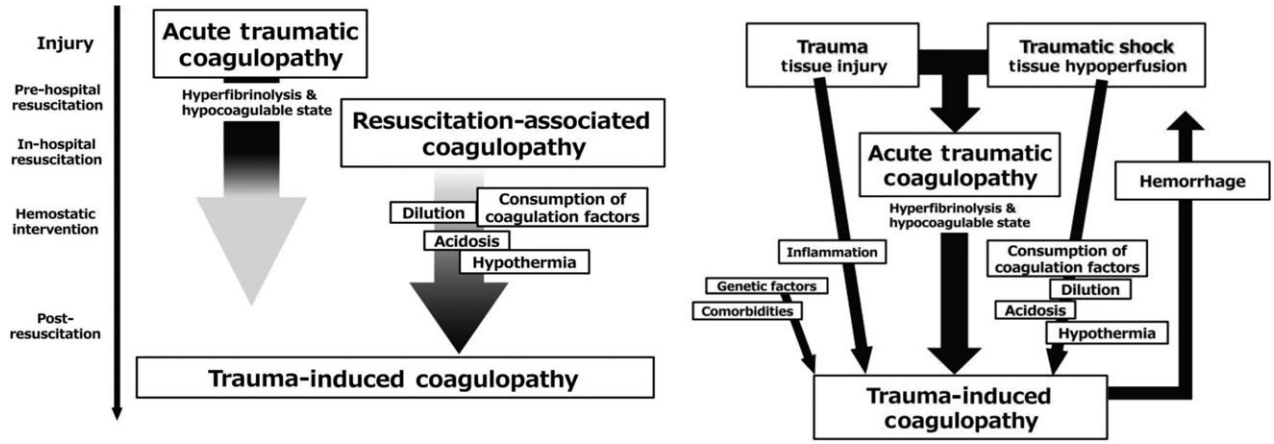

Fig. 1. Pathophysiologic response timeline and the trauma-induced coagulopathy dynamic.[1]

causing coagulation factor deficiencies due to tissue injury or hypoperfusion. The second phase follows therapeutic factors given to the patient during resuscitation.[22] For example, major blood loss causes vasoconstriction in the surrounding vessels in part due to norepinephrine and epinephrine being released by the body. When medical intervention occurs to combat the bleeding, this response is counteracted and catecholamine secretion is diminished, as if the bleeding is controlled, causing the patient's physiology to work against hemostasis. This is why rapid hemostasis is so important, and it also highlights the importance of using proper ratios of blood products in resuscitation. Notably, the recent PROPPR study found that early administration of plasma, platelets, and PRBC in a 1:1:1 ratio instead of a 1:1:2 ratio achieved hemostasis faster and patients experienced decreased mortality by exsanguination.[23] The third phase, post-resuscitation, is acute and leads to a prothrombotic state which predisposes venous thromboembolism. If resuscitation takes place later or is done poorly, disseminated intravascular coagulation can occur.[22]

Although it is an influencing factor of TIC, the disruption of the normal fibrinolytic pathway is not widely understood. When treating coagulopathy, many worry about hyperfibrinolysis without considering the possibility of fibrinolytic shutdown. It has surprisingly been found that, when investigating the fibrinolysis spectrum, fibrinolytic shutdown was most common (46%) with hyperfibrinolysis only accounting for 18% of fibrinolysis patients. These findings raise a need for caution when using antifibrinolytics to treat TIC.[24]

As shown here, coagulopathy of trauma is multifactorial. It can be changed by dilution of hemostatic factors, crystalloid and colloid.[7] Coagulopathy can be made worse by hemorrhagic shock, metabolic acidosis, hypothermia, hyperfibrinolysis, hypocalcemia, and anemia. It is important to note that TIC can present in absence of acidosis and hypothermia; however, coagulopathy can be predicted by persistent hypothermia or acidosis.[7] If this remains uncorrected, the triad will continue to feed on itself in a so-called "vicious cycle".

Interventions

Trauma-induced coagulopathy represents a distinct entity, and is different from other coagulation abnormalities. Traditionally, tests to diagnose TIC were the same as the tests that assess other forms of coagulopathy; this included international normalized ratio/prothrombin time (INR/PT) and activated partial thromboplastin time (aPTT). It is important to realize the limitations of these diagnostic tests. Prothrombin time measures the time it takes plasma to clot when exposed to a tissue factor; INR is then the ratio of patient PT to control PT. Activated partial thromboplastin time measures the time it takes plasma to clot when exposed to substances that activate contact factors.[25] It has been found that INR/PT is more reliable in the traumatic setting due to the possibility of false positives with aPTT.[26] In addition, both INR/PT and aPTT are not typically available for initial trauma assessment and only measure the fluid phase of coagulation without taking platelets or fibrin into consideration.[27] Fibrinolysis can be measured by fibrin or fibrinogen degradation products. However, these assays do not differentiate between fibrin and fibrinogen.[28]

Viscoelastic tests evaluate cellular and protein components of hemostasis as well as fibrinolysis. They are dynamic tests that analyze fibrin formation, breakdown, clot strength, and fibrinolysis opposed to just the end-point of fibrin formation.[29] Because of this, viscoelastic tests can guide coagulation therapy in a faster, more efficient way in order to detect which patients are most at risk for developing coagulopathy and will require mass transfusions.[9,11] Individual hemostatic coagulation management using viscoelastic tests can reduce the risk of undertransfusion (increased bleeding risk) and overtransfusion (increased acute respiratory distress, lung injury, sepsis, and multiple organ failure(MOF)).[11] Previous methods addressing this have been expensive and time-consuming. As most deaths associated with traumatic bleeding occur within the first 6 h, viscoelastic testing could improve patient outcomes.[9]

Both TEG and ROTEM are types of viscoelastic tests. In TEG, patient blood along with calcium and an activator are added to a cup and rotated. The results are then read electronically. In ROTEM, the pin rotates and change in movement is detected optically.[29] Transfusion algorithms regarding TEG recommend plasma, whereas ROTEM recommends fibrinogen.[30]

Thromboelastogram-directed resuscitation was found to be effective in MTP resuscitation. Massive transfusion protocol without TEG showed increased mortality.[6,31] A randomized clinical trial at a level I trauma center found that in the MTP–conventional coagulation assays) group, more plasma and platelets were needed in the first 2 h of resuscitation.[6]

Recently, a platelet-specific TEG test, TEG platelet mapping, has been developed. This technique analyzes platelet function as well as specifically measuring platelet contribution to the strength of the clot. As platelet function and coagulation are interwoven processes, TEG platelet mapping measures both processes in one test.[32] Because hemorrhagic shock leads to activation of the plasminogen pathway, the addition of tPA to the currently available TEG produces results faster than conventional methods. The combination of INR followed by tPA–TEG identified 97% of patients

who did not require blood products, significantly reducing waste. This combination also improved the ability to predict who will require a transfusion by 40%.[33]

Fibrinogen deficiency was usually the initial abnormality in severe trauma patients.[5] When comparing fibrinolysis phenotypes, 46% had fibrinolytic shutdown. This is associated with increased mortality.[23] The most efficient tools to assess fibrinolytic activity are viscoelastic tests, TEG and ROTEM.[34–36] Some authors questioned the use of TEG and ROTEM and found shortcomings in their clinical applicability.[37] There might also be practical barriers to using viscoelastic tests, as interpretation of results is less than straightforward. Familiarity of these methods is important to ensure proper use.

Trauma-induced coagulopathy is targeted by delivering FFP, platelets, and other high-dose blood components early. The effectiveness of each component independently correcting TIC appears to be widely unknown. One site-specific study did note that high-dose FFP alone had no obvious benefit and that standard dose blood components did not correct TIC during hemorrhage. A combination of high-dose FFP, platelet and cryoprecipitate therapy, along with a high total fibrinogen was found to improve coagulation.[12] To correct TIC, FFP has generally been the mainstay of treatment, and is often empirically given in massive transfusion situations, particularly to treat coagulation abnormalities;[38] however, there is some evidence that concentrated factors, such as prothrombin complex concentrate, could be equally or more efficacious.[39] In this interesting study, patients who sustained major blunt traumas that received solely fibrinogen and prothrombin complex concentrate as treatment (CF group) were compared with patients who received the combination of CF and FFP as their treatment (FFP group). The CF group had a quicker restoration of hemostasis and required significantly fewer RBC and platelets in comparison to the FFP group. Also, fewer patients in the CF group developed MOF. Giving FFP had no benefit in restoring hemostasis but was associated with significantly higher transfusion rates for RBC and platelets.[39] Currently, this is not standard treatment, but other groups have found better results in combining them with FFP than FFP alone.[40] A recent intriguing study from Japan also noted a therapeutic effect of high-dose factor XIII in a human *in vitro* and rat *in vivo* model.[41]

The need for a standard of blood product ratios to be utilized in patients who were rapidly bleeding and thus required large amounts of blood products prompted numerous studies. Although it is difficult to do prospective studies on trauma patients, the PROMMTT study found that higher plasma and platelet ratios given early in resuscitation led to decreased mortality.[42] An early massive transfusion using a 1:1 ratio of plasma : RBC was shown to decrease coagulopathy[8] and death from hemorrhage.[7] Trauma patients who were transfused less plasma relative to RBC had lower rates of survival. To combat this, it is recommended that MTP be invoked as early as possible, and, along with a more aggressive use of plasma, this should control coagulopathy more efficiently.[5] This would then require less crystalloid and RBCs in the first 24 h of resuscitation leading to a decrease in the development of dilution-associated coagulopathy.[4,7] Coagulopathy can also be treated with a 1:1:1 ratio of PRBC : FFP : platelets.[4,13] This 1:1:1 ratio was found to decrease early crystalloid use and mortality.[13] The landmark PROPPR study found that a 1:1:1 ratio of FFP : platelets : PRBC reduced early mortality from hemorrhage compared to the 1:1:2 ratio.[23] Although overall mortality has not significantly changed, there has been a rising trend in the past decade for increased use of blood products designed to treat coagulopathy prior to clinical manifestation.[4] However, a conflicting study found that a 1:1:1 driven MTP (RBC : plasma : platelet) did not affect the nature, duration, or frequency of coagulopathy.[5] The results of these studies indicate a complex, multivariable relationship between the simple restoration of the clotting system, coagulopathy, and mortality.[5,8]

In addition to blood ratios, there have been other therapeutic advances to regulate TIC. Recombinant factor VII is one method of controlling TIC. Factor VII works by converting prothrombin to thrombin in the presence of a tissue factor and causes thrombin to burst on the surface of the platelet. A control trial on factor VII was carried out and it was found to significantly reduce blood transfusion necessity for patients with hemorrhagic shock from blunt trauma. Similar trends were found in penetrating trauma; however, they were not significant.[43] A recent addition to hemorrhage intervention is tranexamic acid (TXA). Tranexamic acid had been used to reduce transfusion requirements in patients undergoing elective surgery. The CRASH-2 trial studied the effectiveness of TXA on blood transfusion and death in trauma patients. If TXA is given within 3 h, both mortality and risk of death due to bleeding were found to be significantly reduced.[44] Similar results were found in a trial of military casualties who had received TXA; interestingly, the benefit of TXA was most striking in those patients who received massive transfusions, leading to the speculation that patients in more profound shock have the best chance of benefitting from fibrinolysis inhibition.[45]

Massive transfusion protocols

Because of the need for multiple factors as well as rapid blood replacement in a patient with substantial or

exsanguinating hemorrhage, most institutions who treat critically injured patients have adopted MTP.[46,47] Massive transfusion is defined when: (i) total blood volume is replaced within 24 h, (ii) 50% of total blood volume is replaced within 3 h, or (iii) rapid bleeding rate is documented or observed.[48] Guidelines have been published for the use of the MTP.[49] Part of the goal of the MTP would be expected to prevent and treat trauma-related coagulopathy, and indeed several MTP protocols have been published that use the coagulation tests as a guide for administration of coagulation factors and adjuncts to manage this problem.[38] It is important to realize that an improperly executed MTP can worsen coagulopathy due to dilution and thrombocytopenia, which, again, heightens the importance of correct administration of

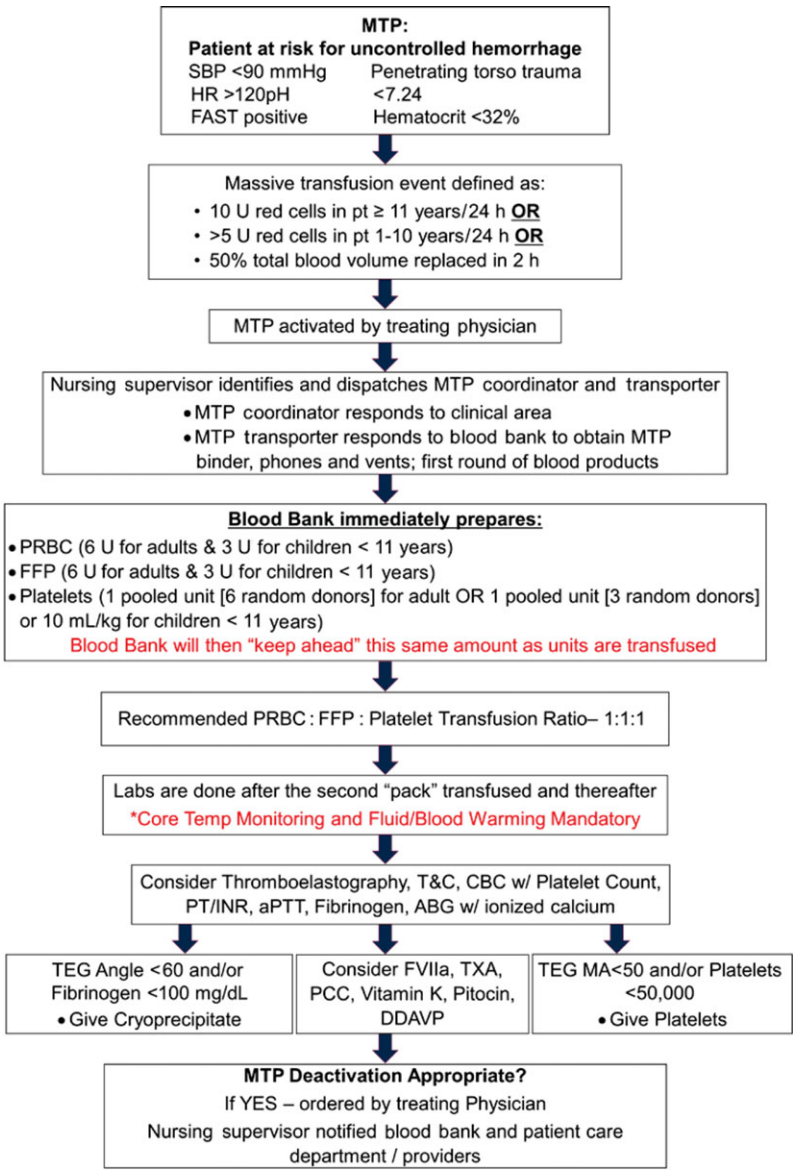

Fig. 2. Crew resource management for an massive transfusion protocol (MTP) activation. ABG, arterial blood gas; aPTT, activated partial thromboplastin time; CBC, complete blood count; DDAVP, Desmopressin (1-deamino-8-D-arginine vasopressin); FAST, focused assessment with sonography in trauma; FFP, fresh frozen plasma; HR, heart rate; PRBC, packed red blood cells; PCC, prothrombin complex concentrate; PT/INR, prothrombin time/international normalized ratio; SBP, systolic blood pressure; T&C, type and cross; TEG, thromboelastography; TEG MA, thromboelasgraphy maximum amplitude; TXA, tranexamic acid.

blood and blood products and liberal use of adjuncts such as TXA, as well as frequent testing to assess the degree of coagulopathy and clot formation.[48] Integration of more advanced coagulation testing into MTP, however, is currently suboptimal.[50]

A special issue arises when the MTP is activated in hospitals that do not use it as often as major urban trauma centers but still treat patients that need massive transfusion. How best to implement this is not entirely clear. Recently our institution has utilized the principle of crew resource management (CRM). The technique of CRM was first established by the aviation industry due to the finding that most mistakes were a result of a lack of communication and coordination rather than the mistakes of the individual. Crew resource management training involves skill development in briefing, inquiry, assertion, vigilance, conflict resolution, and workload distribution. It also creates an organizational environment where cooperation and communication are necessary.[51] Due to the similarity in fast-paced environments and collaborative teamwork, this has been adapted to the health-care field. Crew resource management has been shown to reduce mortality compared with non-CRM institutions. In a national study in the UK with facilities that do not have CRM protocols, blood component therapy delivery was inconsistent and below recommended thresholds.[10] At Penn Medicine Lancaster General Health, a study was undertaken to assess opportunity for improvement of their MTP. An internal review of all trauma patients who underwent MTP in 2016 ($n = 25$) uncovered 11 instances of MTP-related issues. As a direct result, a standard training procedure known as CRM was implemented in an effort to decrease the occurrence of communication errors and ultimately improve patient outcomes. Mortality was reduced after the implementation of CRM, although the results were not statistically significant (0.32 (in 2016) versus 0.24 (2017); $P = 0.597$).[52]

CONCLUSION

ALTHOUGH TRAUMA -related coagulopathy is a serious and often lethal condition, it is amenable to prevention and treatment, providing bleeding control is obtained.[1–3] As coagulopathy is present in 25–35% of trauma patients, in an effort to prevent these deaths, familiarity with the pathophysiology of ATC and TIC is essential in treatment for trauma patients presenting with coagulopathy or any coagulopathy precursors.[1] Knowledge of the clotting cascade and related factors is important in understanding the physiology behind TIC to ensure proper treatment. Although promising, additional studies must be undertaken to assess the effectiveness of fibrinogen and/or prothrombin complex concentrates at regulating TIC. An early MTP with a 1:1 plasma : RBC ratio or a 1:1:1 plasma : RBC : platelets is the current best practice. Some researchers suggest that TEG and ROTEM show promise and have been incorporated in assessing fibrinolytic activity.[18,19,22] Tranexamic acid is also a viable option to reduce coagulopathy and mortality as noted and supported in the CRASH-2 and MATTERS studies.[44] In addition to important diagnostic tests, the timely delivery of blood products and efficiency following an MTP can be improved by implementing a CRM procedure. Further research is needed to refine treatment and care of these patients. Trauma-induced coagulopathy will likely never be entirely preventable; however, if recognized early and understood, it can be treated with improvement in patient outcomes.

DISCLOSURE

Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
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