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Review Article

Acute traumatic coagulopathy: pathophysiology and resuscitation

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Abstract

Acute Traumatic Coagulopathy occurs immediately after massive trauma when shock, hypoperfusion, and vascular damage are present. Mechanisms for this acute coagulopathy include activation of protein C, endothelial glycocalyx disruption, depletion of fibrinogen, and platelet dysfunction. Hypothermia and acidaemia amplify the endogenous coagulopathy and often accompany trauma. These multifactorial processes lead to decreased clot strength, autoheparinization, and hyperfibrinolysis. Furthermore, the effects of aggressive crystalloid administration, haemodilution from inappropriate blood product transfusion, and prolonged surgical times may worsen clinical outcomes. We review normal coagulation using the cell-based model of haemostasis and the pathophysiology of acute traumatic coagulopathy. Developed trauma systems reduce mortality, highlighting critical goals for the trauma patient in different phases of care. Once patients reach a trauma hospital, certain triggers reliably indicate when they require massive transfusion and specialized trauma care. These triggers include base deficit, international normalized radio (INR), systolic arterial pressure, haemoglobin concentration, and temperature. Early identification for massive transfusion is critically important, as exsanguination in the first few hours of trauma is a leading cause of death. To combat derangements caused by massive haemorrhage, damage control resuscitation is a technique that addresses each antagonist to normal haemostasis. Components of damage control resuscitation include damage control surgery, permissive hypotension, limited crystalloid administration, haemostatic resuscitation, and correction of hyperfibrinolysis.

Key words: coagulation; physiology; resuscitation; transfusion; trauma

For decades, the *art* of medically managing the trauma patient was just that, an *art*. A paucity of scientific information existed until the beginning of Operation Dessert Shield in 1990 when the problem of massive trauma, coagulopathy, and transfusion was thrust prominently into the global spotlight. Since 1990, several studies have demonstrated the endogenous effects of massive trauma (Acute Traumatic Coagulopathy, ATC) and the iatrogenic effects of resuscitation strategies after major trauma (Trauma Induced Coagulopathy, TIC). In addition, physicians interested in trauma have organized into specialized societies (European Society of Trauma and Emergency Surgery, Trauma Anesthesiology Society, British Trauma Society, Eastern Association For the Surgery of Trauma, etc.), lending guidance through consensus statements and protocols. The principles of trauma management should be of concern to *all* anaesthetists, as trauma remains a global epidemic. The United States Centers for Disease Control and Prevention in 2014 ranked unintentional injury as the leading cause of death among ages 1-44.[1] The World Health Organization also reports injuries as leading causes of death, especially for men worldwide.[2] The aim of this review is to provide an update of current understanding of the pathophysiologic

Key points

- Severe trauma can lead to acute traumatic coagulopathy (ATC) by activation of protein C, endothelial glycocalyx disruption, consumption of fibrinogen, and platelet dysfunction.
- ATC increases mortality and morbidity, and requires coordinated treatment based on damage control resuscitation.

changes after major trauma and inform providers of current recommended resuscitation strategies.

Normal haemostasis

An understanding of the normal interaction between the major proteins and cells involved in haemostasis is imperative to understanding the pathophysiological changes that occur in ATC. For decades, our understanding of haemostasis was based on the intrinsic and extrinsic pathways of the coagulation cascade model. This model facilitated understanding of *in vitro* coagulation and interpretation of laboratory tests (prothrombin time and activated partial thromboplastin time); however, it did not fully explain *in vivo* haemostasis. Hoffman and colleagues[3] explained a cell-based model of haemostasis that better described the *in vivo* processes involved in coagulation. This model included three overlapping stages of coagulation: initiation, amplification, and propagation. (Fig. 1)

Initiation

Initiation of coagulation begins with plasma exposure to tissue factor (TF). TF is a membrane protein with a binding domain for factor VII/VIIa on its extracellular portion.[4] A variety of extravascular cells express TF, and plasma of healthy individuals contains TF-bearing microparticles from monocytes, erythrocytes, and platelets.[5] However, normal platelets that have not undergone activation do not express TF. Once there is a tear in the vessel wall, extravascular TF binds to fVII, leading to activation to fVIIa, which forms the activated complex TF/fVIIa.[6] This complex activates fX (to fXa). Factor Xa activates fV (to fVa).[7] Once the TF/fVIIa complex leaves its local environment, it is rapidly inhibited by tissue factor pathway inhibitor (TFPI) or antithrombin III (ATIII).[3]

Amplification

Small amounts of thrombin are produced by the activated fXa/fVa complex.[8] This, along with exposure to extravascular proteins, allows for platelet adhesion and activation. Platelets further release fV (that will be activated by and complex with fXa). Activated platelets bind von Willebrand Factor (vWF)/fVIII, cleave fVIII from the vWF, and activate it to fVIIIa.[9] Once fVa and fVIIIa are bound to the platelet surface, propagation begins.

Propagation

TF/fVIIa complex activates fIX. Activated fIX binds fVIIIa on the platelet surface to form the tenase complex. This complex (fVIIIa/fIXa) further activates fX on the platelet surface. The increased fXa binds to fVa on the platelet surface to produce a thrombin burst for clot formation.[3]

Inactivation

There are several mechanisms in place to prevent widespread coagulation away from the site of injury. ATIII binds and inhibits thrombin. A receptor that is present on healthy endothelial cells, thrombomodulin (TM), also binds thrombin.[10] This thrombin/TM complex activates Protein C on the endothelial surface, and Activated Protein C (APC) binds with Protein S. The APC/Protein S complex inactivates fVa and fVIIIa on the surface of endothelial cells.[3] Thus, thrombin switches into an anticoagulant protein as opposed to a procoagulant when combined with TM on the endothelial cell surface.

Key points

The cell-based model highlights the major role that platelets play in normal haemostasis as a surface for factor interaction, activation, and ultimately the generation of thrombin. In addition, as a result of various mechanisms, thrombin generation and clot formation occur locally at the site of injury without widespread dissemination of clot, which includes altering the properties of thrombin (when combined with TM) to become an anticoagulant.

Pathophysiology of acute traumatic coagulopathy

Activated protein C

The proenzyme protein C circulates in plasma and becomes activated once it interacts with the thrombin/TM complex on the endothelial cell surface. This is facilitated through the membrane protein, endothelial protein C receptor (EPCR).[11] Once activated, protein C produces an anticoagulant effect through several mechanisms: reduced thrombin formation by inactivation of fVa and fVIIIa, and increased fibrinolysis through inhibition of plasminogen activator inhibitor 1 (PAI1).[11–13]

Many studies have validated the essential role that APC plays in ATC. In a subset of patients from the PROMMTT (Prospective, Observational, Multicenter, Major Trauma Transfusion, 2013) study that had coagulation factor analysis performed, Cohen and colleagues[14] found that in severely injured patients with shock, APC concentrations were increased and coagulation factors, including factors V and VIII, were depleted. Other studies have yielded similar findings with high concentrations of soluble thrombomodulin in combination with low protein C concentrations (an indirect measurement of APC), or directly measured high APC concentrations in severely injured patients with elevated base deficits. These findings were associated with increased mortality, organ injury, transfusion requirements, and reduced ventilator-free days.[12 15] With selective APC inhibition, early traumatic coagulopathy is prevented in mice.[16]

Although APC appears to be an important component for the development of ATC, there is conflicting evidence presented in *in vitro* studies. Campbell and colleagues found that platelets and fVa are resistant to cleavage by APC and that APC had no detectable effect on fibrinolysis.[17] However, Howard and colleagues demonstrated coagulation disturbances on thromboelastography (TEG) consistent with ATC with the addition of APC alone.[18]

With its ability to reduce fVa and fVIIIa concentrations and induce fibrinolysis, APC appears to be part of the multifactorial process that leads to ATC. Studies *in vivo* have demonstrated that increased concentrations of APC lead to clinical findings of

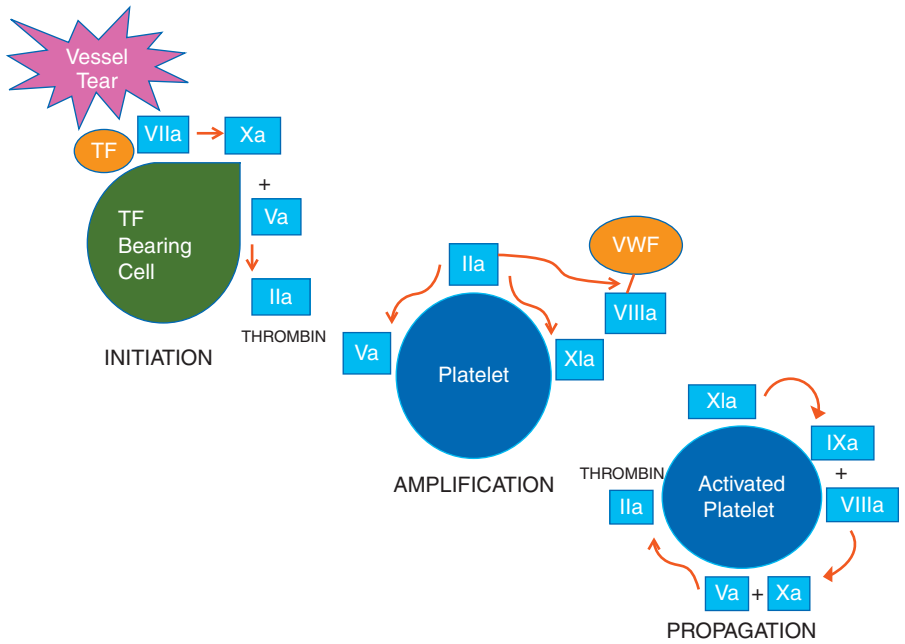

Fig 1 Cell based model of haemostasis.

ATC, along with increased transfusion requirements and death. Because of this, APC is believed to be a major contributor to ATC. Further investigations are warranted to understand its importance in targeted treatments for improved patient outcomes.

Endothelial glycocalyx

The endothelial glycocalyx (EG) is a heterogeneous group of proteoglycan core proteins linked with glycosaminoglycan chains that line the luminal side of the vascular endothelium.[19] A common proteoglycan in the EG is syndecan-1. It has been extensively studied, and serum concentrations correlate with EG destruction.[20] Several factors specifically related to trauma with shock disrupt the EG: tissue trauma, hypoperfusion, catecholamine surge, and inflammation.[21 22] Evidence supports EG destruction as an important mediator in the development of ATC. Potential mechanisms of ATC induced by EG destruction are discussed below.

The first mechanism is autoheparinization. Heparan sulfate, a prominent glycosaminoglycan in the EG, is released into the circulation upon disruption of the EG. Its heparin-like property leads to anticoagulation.[15 23 24] Secondly, it is believed that disruption of the EG is linked to the APC pathway. Johansson and colleagues[22] showed that significant endothelial glycocalyx destruction led to increased soluble TM, reduced protein C concentrations, hyperfibrinolysis, and prolonged activated thromboplastin time (aPTT). Increased soluble TM and low protein C concentrations correlated with high concentrations of APC, which suggested there was significant overlap between EG destruction and the APC pathway in the development of ATC. However, when this same group directly measured APC concentrations in trauma patients, they came to a different conclusion. They found that in patients with more severe injuries, there was a greater degree of EG disruption. In this subset of patients, there was a greater degree of heparinization measured by TEG. Patients with more severe injuries and EG destruction also had greater degree of hyperfibrinolysis, higher TM concentrations, and a lower measured protein C concentration. However, when APC was measured, there was no significant difference between groups. Therefore, the APC pathway was not thought to be responsible for the coagulation changes.[25] These studies also showed increased transfusion requirements in patients with elevated syndecan-1 concentrations,[22 25] and higher mortality in trauma patients with higher syndecan-1 concentrations.[25]

Only recently has the importance of the EG been demonstrated. The EG plays a vital role in many physiologic and pathophysiologic processes, such as ATC. This area of research has great potential for better understanding of ATC and targeted treatments.

Fibrinogen

A major component of the haemostatic pathway, fibrinogen is critical to clot formation. Fibrinogen contributes to clot formation by two mechanisms: by facilitating aggregation of platelets via the glycoprotein IIb/IIIa receptor and by forming a network of fibrin strands that stabilizes the clot.[26] Fibrinogen is an acute phase protein present at high concentrations (1.5 to 4.0 g L^{-1}). Significant depletion occurs early in ATC[26–28] as a result of reduction in fibrinogen production and accelerated breakdown or hyperfibrinolysis. Decreased production of fibrinogen occurs in patients with hypothermia of 32°C.[27] Hyperfibrinolysis can occur because of increased release of tissue plasminogen activator (t-PA) and/or reduction of PAI-1 (via APC pathway).[14 29] Recently, Moore and colleagues[30] showed red blood cell (RBC) lysate from haemolysis contributes to fibrinolysis.

In the trauma setting, low admission fibrinogen concentrations are associated with increased trauma severity,

hypoperfusion, and pre-hospital fluid administration.[31 32] Low fibrinogen concentrations also correlate with increased transfusions, reduced ventilator-free days, and increased one and 28-day mortality.[29 32] Multiple pathways and triggers can lead to hypofibrinogenaemia in ATC. Again, there is potential overlap with other mechanisms of ATC – APC inhibition of PAI-1.

Platelet dysfunction

The cell-based model of haemostasis described above stresses the importance of platelets as a surface on which interaction and activation of multiple factors occur.[3] Platelets contribute more to clot strength compared with fibrinogen (69 vs. 31%) after a trauma.[33] Despite alterations in function, ATC patients typically have normal platelet counts on admission. Kutcher and colleagues[34] found the mean platelet count on admission in 101 trauma patients, however, 45% of these patients demonstrated "platelet hypofunction." Wohlauer and colleagues[35] also noted a normal mean admission platelet count in trauma patients, and that 86% of these patients had ADP inhibition of platelet function. By comparison, only 4.2% of healthy volunteers had ADP inhibition. They described this phenomenon as "exhausted platelet syndrome" from initial platelet hyperactivation as a result of widespread ADP release from injured endothelial cells. This initial activation renders platelets unresponsive – despite an adequate number – to subsequent stimulation. ADP inhibition appears to contribute to hyperfibrinolysis through the t-PA pathway.[36]

Despite being quantitatively normal on admission, trauma patients have increased in-hospital and 24-h mortality rates when there is detectable platelet dysfunction.[34] Patients with higher absolute platelet counts on admission had increased survival; however, both groups still noted high mortality rates in patients that had normal platelet counts on admission.[37 38] These findings not only reflect the important role that platelets play in ATC, but also highlight the fact that normal admission platelet counts do not correlate with adequate function.

Classic trauma triad—haemodilution, hypothermia, and acidaemia

Three major factors that are associated with subsequent development of trauma-induced coagulopathy (TIC) after injury are haemodilution, hypothermia, and acidaemia. In a subset analysis of PROMMTT patients, prehospital crystalloid administration, base deficit $<$-6, and hypothermia [35.8 (1.2)°C] on admission were independent risk factors for development of TIC.[14] A review of the German Trauma Registry database found that pre-admission crystalloid resuscitation was associated with coagulopathy and that the incidence of coagulopathy increased with increasing amounts of crystalloid administered.[39]

The effects of hypothermia on the coagulation system involves some controversy. Scharbert and colleagues[40] presented evidence that platelet aggregation is increased at mild to moderate hypothermia (30-34 °C), suggesting that bleeding in this population is not a consequence of platelet dysfunction. Wolberg and colleagues[41] noted a significant reduction in both platelet function and coagulation enzyme activity at temperatures below 33 °C. Mitrophanov and colleagues[42] demonstrated impaired thrombin generation in hypothermia and an inverse correlation between thrombin generation and temperature.

The development of acidaemia also plays a critical role in TIC. In a swine model, the initiation of acidaemia (pH 7.1) resulted in depletion of fibrinogen by 34% and platelet count by 51%. Thrombin generation in the propagation phase was decreased by nearly 50% as well. This correlated with significant prolongation in PT, PTT, and ACT and a significant decrease in the alpha angle and maximum amplitude on TEG.[43] Not only are these factors associated with TIC, but they are also associated with increased mortality. A retrospective review of 38,520 trauma patients found that hypothermia was an independent risk factor for mortality (odds ratio, 3.03; 95% CI, 2.62-3.51).[44] In another retrospective analysis, non-survivors of trauma were likely to have a lower core body temperature and pH.[45] These findings underscore the importance of understanding and treating preadmission "classic triad" in an effort to reduce both TIC and mortality. (Fig. 2)

Resuscitation strategies in acute traumatic coagulopathy

Massive transfusion triggers

Recognizing a patient in extremis may seem straightforward, however, with the use of specific triggers for Damage Control Resuscitation (DCR), the art of early identification becomes more scientific. A retrospective validation study of triggers for massive transfusion (MT) using the PROMMTT study dataset, revealed five strong predictors of massive transfusion and DCR.[46] The two strongest predictors for MT in the first 6 h were INR $>$1.5 (OR 5.8, CI 4-8.2, $p < 0.0001$) and Base Deficit $\leq$6 (OR 4.5, CI 3-6.9, $p < 0.0001$). Of note, viscoelastic coagulation tests were not used in this analysis yielding limitations. Notably, thromboelastometry parameters have similar predictability.[47] Other strong predictors included systolic arterial pressure $<$ 90 mm Hg, haemoglobin $<$ 11 g dL^{-1}, and positive Focused Assessment with Sonography in Trauma exam (FAST). The weaker predictors included heart rate $>$ 120 bpm and penetrating injury. When combined into a massive transfusion score (MTS), a linear relationship is seen for massive transfusion. This method of identification is both sensitive (MTS $>$ 2, 85% sensitivity of MT in 24 h) and has a high negative prediction value (MTS $<$ 2, NPV 89% not receiving MT). In a study of the MTS system, hypothermia $<$ 35.5°C was added and positive FAST, mechanism of injury, and heart rate were removed from the score making it identical to the Cincinnati Triggers.[48 49] Massive transfusion scoring systems have also been developed with clinical predictors that include age $>$ 60 yr, blood lactate $>$ 2.5 mmol L^{-1}, pelvic injury, femur fracture, and clinical suspicion.[50–52] Systems using weighted points tend to require special calculators and may slightly delay initiation of MT, but they have better predictive capabilities. The key point is that early recognition of the patient needing MT is critical because of the unique strategy for resuscitation and the environment in which they must be resuscitated. (Table 1) While scoring systems can lead to earlier identification, a limitation is that they cannot distinguish the actual pathomechanism of the bleeding.

Certain populations of trauma patients display exaggerated coagulopathy as a result of mechanisms beyond the scope of this review. Pregnant patients can present with a clinical syndrome similar to disseminated intravascular coagulation because of placental disruption.[54] Traumatic brain injury patients release large amounts of tissue thromboplastin into their circulation, compounding coagulopathy.[55] Burn patients develop an acute burn induced coagulopathy.[56] Finally, an increasing number of trauma patients are found to be taking anticoagulants for a variety of medical disorders.[57]

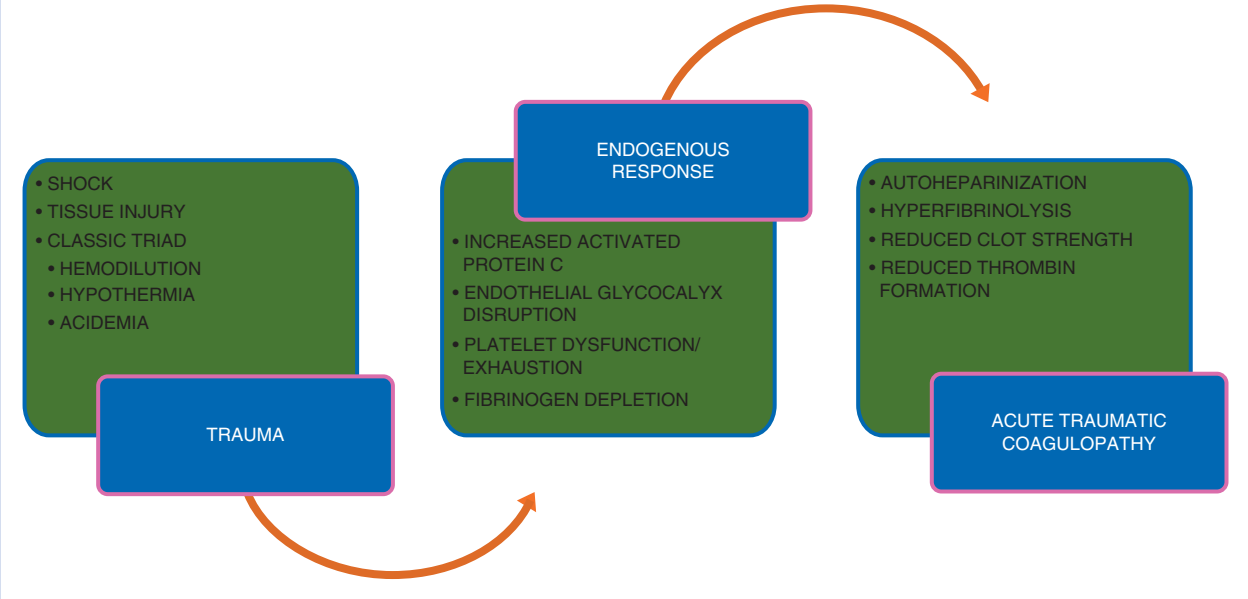

Fig 2 Acute traumatic coagulopathy.

Table 1 Comparison of massive transfusion scoring systems after major trauma.[4648* 5052* 53] INR: International normalized ratio, MTS: Massive Transfusion Score, rMTS: Revised Massive Transfusion Score, CITT: Cincinnati Individual Transfusion. Trigger, SAP: systolic arterial pressure, TBSS: Traumatic Bleeding Severity Score, ABC: Assessment of Blood Consumption, TASH: Trauma Associated Severe Haemorrhage, MT: Massive Transfusion, AUROC: Area Under Receiver Operator Curve

	MTS	rMTS/CITT	TBSS	ABC	TASH
INR	>1.5	>1.5			
Base Deficit	≤ -6	≤ -6			< 2
SAP (mm Hg)	< 90	<90	< 110	<90	< 120
Haemoglobin (g dL^{-1})	< 11	<11			< 12
FAST Exam	+		+	+	+
Mechanism	Penetrating			Penetrating	
Age (yr)			> 60		
Lactate (mmol L^{-1})			> 2.5		
Pelvic Fracture			Type A-C		Unstable
Femur Fracture					Open Dislocated
Heart Rate (beats min^{-1})	> 120			>120	> 120
Temperature (°C)		<35.5			
Sex					Male
Weighted Points	–	–	+	–	+
Predicting MT AUROC	0.7	0.72 (MT at 24 h)	Score > 15, 0.985	0.859	0.905

Technique and strategies

The technique of Damage Control Resuscitation (DCR) can be broken into components: damage control surgery, rapid rewarming, permissive hypotension, limited crystalloid transfusion, physiology-based or ratio-based blood component therapy, and correction of hyperfibrinolysis. All trauma resuscitation strategies have the common goals to stop bleeding, reestablish haemostasis, and restore normal perfusion pressure. Both micro- and macrocirculation should be considered when monitoring for "normal perfusion": Haematocrit, haemoglobin, serum lactate, and base deficit for monitoring microcirculation and dynamic indices and noninvasive cardiac output monitors for macrocirculation.[58] When to use DCR and when to transition from DCR to traditional medical care is an emerging field of study. (Fig. 3)

Damage control surgery

The principles of Damage Control Surgery (DCS) should be to control haemorrhage, limit contamination, and temporize rather than seek definitive therapy of all trauma injuries. After an abbreviated procedure, that often includes temporary

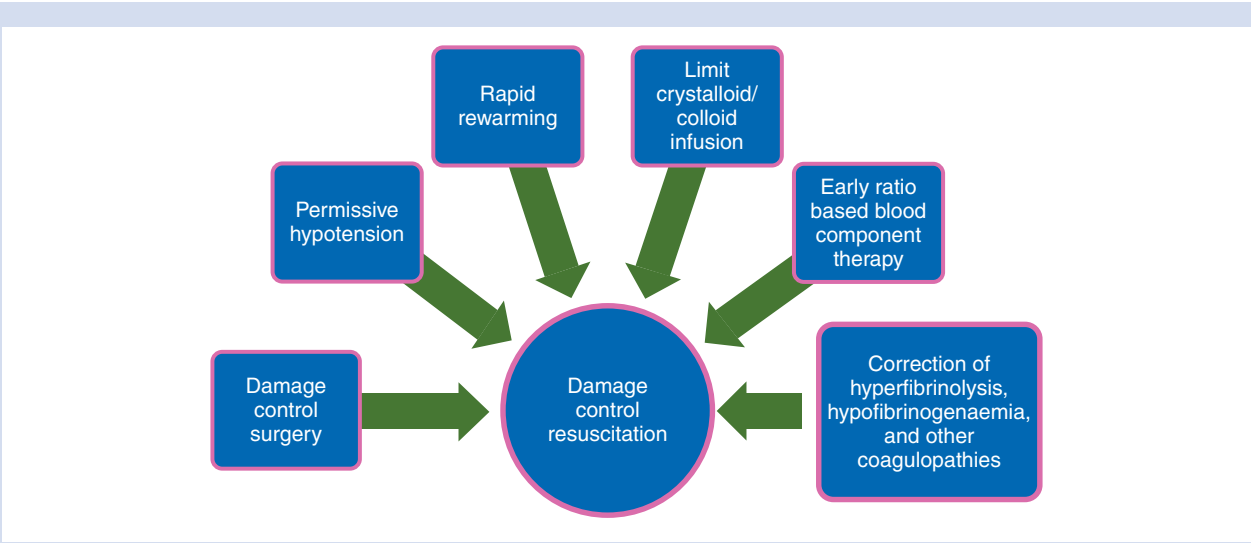

Fig 3 Tenants of damage control resuscitation.

abdominal closure, peri-hepatic packing, vena cava examination, resection of injured bowel, and/or external-fixation of fractures, the patient is transported to an intensive care unit (ICU) for correction of hypothermia and ongoing resuscitation. A retrospective cohort study of 390 patients in 2011 revealed that combining damage control laparotomy (DCL) with other tenants of DCR reduced crystalloid, red blood cell (RBC), plasma, and platelet transfusion volumes. Additionally, DCL aided in reducing severe acidaemia, hypothermia, and coagulopathy upon arrival to the ICU (80% vs. 46%, $p < 001$).[59] The surgeons in this study used clinical suspicion to identify patients requiring DCL. The published indications for DCS were developed in 1998 and include inability to achieve haemostasis, inaccessible major vascular injury, time-consuming procedure in a sub-optimally resuscitated patient, life-threatening extra-abdominal injury, inability to reapproximate abdominal fascia because of oedema, and reassessment of intra-abdominal contents.[60] A balance must be maintained, with careful selection of patients requiring DCS vs those that are stable enough to undergo definitive repair possibly limiting reoperations, reducing ICU burden, and reducing complications associated with DCL. These include readmissions, intra-abdominal infection, fistula formation, and abdominal wall hernias.[61 62]

Operationally, it is important for the anaesthetist to prepare for DCR. The operating theatre should have ready access to equipment and be spacious enough for multiple providers to interact. Dedicated trauma operating rooms should have their own supply storage racks containing i.v. catheters, fluids, tubing, etc. Along with haemodynamic monitors, i.v. access in the form of two large bore peripheral catheters is preferentially obtained before arterial access for bp monitoring. Additionally, access to video laryngoscopy and ultrasound should be immediately available. Checklists and cognitive aides have been created to prepare for trauma anaesthesia.[63 64]

An aspect of trauma resuscitation that has not been clearly elucidated is the optimal choice of anaesthetic technique. Conventionally, volatile anaesthetics that vasodilate a critically hypotensive patient have been avoided until resuscitation proves adequate. I.V. techniques that use multimodal analgesia (opioids, NMDA glutamate receptor antagonists), have utility as initial anaesthetics for trauma patients and provide analgesia and amnesia. Regional techniques have usefulness, but might not be timely enough and could mask compartment syndromes. Analgesia through multiple phases of trauma is an important concept and has important implications to reduce chronic pain syndromes.[65]

Rapid rewarming

As detailed earlier, severe hypothermia impairs thrombin generation and contributes to platelet dysfunction. Management techniques can be divided into passive rewarming, active external rewarming, and active internal rewarming. As DCR relies on rapidly rewarming the trauma patient, all of these techniques are used in concert. Active external rewarming begins with reducing convective, radiant, and conductive heat loss. The trauma patient should be covered at all times unless being examined or treated. This is critically important during transport to and from radiology suites and to the operating room. Temperature in trauma rooms are traditionally kept elevated (23-26 °C) to mitigate intraoperative heat loss, however this might not have significant impact on maintaining normothermia.[66] Fluid warmers and forced air warmers are prepositioned and seem to have a larger impact on heat loss.[67] The patient's trunk is preferentially warmed as warming vasoconstricted extremities can have limited effect. As the skin preparation for trauma surgery often includes the entire body ("chin to knees"), full-underbody, forced-air warmers can be used. Active internal warming uses rapid transfusion and fluid warming devices such as the Level 1 (Smiths Medical, USA) or Belmont Rapid Infuser (Belmont, USA). These should be immediately available and may be primed quickly to warm blood products traditionally stored at 4°C. Recently, cardiopulmonary bypass and extracorporeal membrane oxygenation (ECMO) has resurfaced as a possible treatment for profound accidental hypothermia.[68] Several limitations exist for this therapy in trauma, as it requires a constant infusion of heparinized blood and correction of internal

bleeding sources.[69] Perlman and colleagues[70] have recently developed a trauma guideline for prevention of hypothermia.

Permissive hypotension

Two phases exist describing injury and haemorrhage in trauma: early, active, surgically uncontrolled bleeding and post-surgically controlled repair. During the active phase of bleeding, several animal models and a few prospective human studies have demonstrated reduced bleeding and improved survival when managed with lower transfusion volumes and lower mean arterial blood pressure. This is known as haemostatic resuscitation or controlled/permissive hypotension. The lower limit of arterial pressure is what is now debated. Recent data for controlled hypotension in non-trauma patients comes from orthopaedic and spine surgery and suggests systolic arterial pressure (SAP) of 80-90 mm Hg is safe and reduces blood loss.[71] Schreiber and colleagues[72] randomized 192 trauma patients into traditional care (maintain SAP > 110 mm Hg), or controlled care (transfused only if a radial pulse was lost or SAP < 70 mm Hg). They found no difference between groups in renal injury or ventilator and ICU free days. There was survival benefit for blunt abdominal injuries with a reduced mortality (3% controlled care vs 18% traditional care). There was no mortality difference in patients with penetrating trauma (both 9%). A study of controlled hypotension in penetrating trauma evaluated the difference between MAP 50 mm Hg vs MAP 65 mm Hg during laparotomy and thoracotomy for control of haemorrhage.[73] Though secondary outcomes of myocardial infarction, renal injury, and stroke were similar, there was no survival benefit for the lower MAP group, however, the target MAP for the lower MAP group was not statistically different than the higher MAP group [65.5 (11.6) vs 69.1 (13.8), p = 0.07].[73]

Controlled hypotension is controversial in patients with concurrent traumatic brain injury (TBI) and coronary artery disease. Chestnut and colleagues[74] described a 150% increase in mortality when patients with TBI had SAP < 90 mm Hg. As most studies that investigated controlled hypotension excluded patients with TBI, it is still advised to maintain SAP ≥ 90mm Hg or 20 mm Hg greater than measured intracranial pressure.[75] There is also controversy on the technique used for controlled hypotension. Using restrictive transfusion vs anaesthetic agents to produce lower mean arterial pressures is questioned. Restrictive crystalloid transfusion will be discussed later and appears to have its own benefit. The vasodilating properties of anaesthetic drugs might have benefits after surgical correction of bleeding, but this is not known.

In the face of life threatening hypotension, the European Guideline On Management Of Major Bleeding And Coagulopathy Following Trauma Fourth Edition (2016) now recommends use of vasopressors.[76] Traditionally, vasopressors have been shunned in trauma with uncontrolled haemorrhage, as it could mask true resuscitation efforts and possibly increase mortality. In a secondary analysis of data collected on blunt injured trauma patients, there was an 80% increase in mortality at 12 h and two-fold increase in mortality at 24 h, when vasopressors were used including norepinephrine, vasopressin, phenylephrine, and dopamine.[77] Limited animal studies support use of norepinephrine in uncontrolled haemorrhage with a reduction in transfusion volume and improved survival.[78] In a double-blinded randomized study of 78 patients seeking to limit crystalloid infusion by administering vasopressin, use of vasopressin led to less crystalloid infusion over five days and a lower mortality (13% vs 25%).[79] Finally, trauma patients suffering myocardial dysfunction from contusion, tamponade, or brain injury, can benefit from inotropic support to maintain SAP of 80-90 mm Hg or MAP ≥ 80 mm Hg with TBI. Use of vasopressors remains a highly contested topic that needs further prospective human trials to validate usefulness. Extended haemodynamic monitoring of cardiac output and stroke volume could be extrapolated to trauma patients from recently published recommendations for elective surgery,[80] and might provide more objective means to determine best use of vasopressors.

Limited crystalloid infusion

The goal of limited crystalloid resuscitation must be distinguished from permissive hypotension, as i.v. crystalloid infusion itself can have adverse effects on trauma patients. Aggressive crystalloid fluid administration was once thought beneficial, as it restored normal arterial pressure. Now, many believe that a "resuscitation injury" occurs from excessive crystalloid fluids, including disruption of clot formation, dilutional coagulopathy, glycocalyx disruption, and immunomodulation. In 1,898 patients in the German Trauma Registry, two groups matched based on injury severity, received either low volume (≤ 1.5 L) or high volume crystalloid replacement (>1.5 L) and found that the low volume replacement group was associated with reduced blood transfusion, coagulopathy, and mortality (low-volume: 22.7%, high-volume: 27.6%; $P < 0.01$).[81] In an earlier analysis of the German Trauma Registry of 8724 trauma patients, the amount of crystalloid administered in the prehospital setting correlated with coagulopathy on admission, which was observed in >40% of patients receiving >2 L, in >50% receiving >3 L, and in >70% with >4 L.[39] In a study of 1754 patients, aggressive crystalloid resuscitation had immunomodulating effects and increased morbidity from prolonged ventilator days, ARDS, ventilator associated pneumonia, surgical site infections, and bloodstream infections.[82] Large volumes of normal saline also have detrimental effects causing a hyperchloraemic metabolic acidaemia. This makes utilizing base deficit unreliable as an endpoint of resuscitation.[83] Current best practice is to delay or limit crystalloid fluid to discrete boluses in the prehospital setting, targeted at a lower than normal arterial pressure and maintenance of heart rate. In the hospital setting, providers should limit crystalloid when administering medications and blood products. Intravascular infusions can be administered according to the guidelines from the Association of the Scientific Medical Societies in Germany.[80] In the presence of TBI, arterial pressure should be maintained with MAP ≥ 80 mm Hg. When crystalloid solutions are used, avoid normal saline, and use balanced electrolyte solutions.[76]

Blood component therapy

Despite traumatic injury remaining a leading cause of death worldwide, few prospective randomized studies have been performed to elucidate the best method for haemorrhagic resuscitation.[84] The PROMMTT study revealed improved survival at 6 h, for patients that received higher ratios of plasma to RBC or platelets to RBC. The two most prominent randomized prospective studies to date are the CRASH-2 Trial (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage, 2011) and the PROPPR (Pragmatic Randomized Optimal Platelet and Plasma Ratios, 2016) Study. CRASH-2 revealed a mortality advantage to early use of tranexamic acid (TXA), presumably by mitigating the hyperfibrinolytic response in severely injured patients.[85] The PROPPR study evaluated 1:1:1

(plasma: platelets: RBC) vs 1:1:2 transfusion strategies in 680 severely injured patients (median injury severity score (ISS) 26.5). There was a statistically insignificant 3.7% reduction in 30-day mortality (22.4% vs 26.1%, respectively; [95% CI, −10.2% to 2.7%]; $P = .26$). In addition, patients in the 1:1:1 group achieved earlier haemostasis and had fewer deaths as a result of exsanguination at 24 h (9.2% vs 14.6%, 95% CI -10.4% to -0.5%).[86] With limited RCT evidence to support use of higher plasma and platelet ratios, opponents argue that transfusing patients with higher volumes of plasma products increases acute lung injury, exposes them to transmittable disease, and might not directly address the specific haemostatic abnormality. Complicating the matter, timing of trauma resuscitation is as important as the components used. Opponents of 1:1:1 argue a survivor bias in studies that show a mortality benefit (i.e. a patient still alive to receive higher ratios of platelets and plasma might not have been as severely injured). Finally, there has been great country-specific debate on early use of Ratio-Based Blood Component therapy vs Goal Directed Coagulation Management therapy. For example, Schöchl and colleagues[87] found reduced mortality in trauma patients [ISS 38 (15)] when using thromboelastometry to guide fibrinogen concentrate and prothrombin complex concentrate therapy.[87] Classical coagulation testing is time consuming, reports nonspecific abnormalities, and is generally being replaced by viscoelastic assays in most trauma centers. More rapid assessment of coagulation derangements has been described using thromboelastometry.

To address the issues of how to transfuse the trauma patient a "combined European-American" approach should be used. Ratio-based blood component therapy should be instituted in the initial management of the severely injured patient, until laboratory evidence can be obtained to guide transfusion.[76] A recent randomized control study showed that management of massive transfusion with thromboelastography vs classical coagulation testing resulted in similar RBC transfusion, but less plasma and platelet transfusion. Mortality in the classical coagulation testing group was significantly higher.[88] Correction of coagulation requires knowledge of the pathophysiology of major trauma and should address dilution of coagulation factors, hyperfibrinolysis, depletion of fibrinogen, and inactivation of platelets. To accomplish these goals, providers should seek to deliver factor concentrates, cryoprecipitate, plasma, and platelets early.[89–91] These recommendations are supported in the most recent European Guidelines on Major Bleeding.[76]

Red blood cells and plasma

Based on most recent guidelines, RBC transfusion should target haemoglobin between 7-9 g dL^{-1}.[76] This recommendation is not patient specific and must be increased in patients with a greater demand for oxygen carrying capacity (elderly and cardiovascular disease).[92–94] Other methods to increase haemoglobin such as iron or erythropoetin alpha infusions have not been studied in the acute trauma population. Red blood cells should be warmed and can be rapidly transfused after filtration. Intraoperative cell salvage is used in many trauma centres. Though it may reduce allogenic blood transfusion, its effect on mortality is equivocal.[95]

Plasma should be administered in at least a 1:2 ratio to RBC. Plasma infusions can be warmed and administered rapidly after filtration. Administration of plasma cannot replace or augment fibrinogen concentrations and should not be used as a substitute for this critical clotting factor. Some studies have demonstrated that 1:1 transfusion of plasma: RBC might only prevent worsening, but does not correct coagulopathy.[96 97] Complications associated with plasma administration include transfusion related acute lung injury (TRALI), transfusion associated cardiac overload (TACO), sepsis, and ABO incompatibility. Additionally, thawed plasma's shelf life of approximately five days often leads to waste if unused. With demand for AB-donor plasma increasing, other alternatives have been developed. Liquid Plasma and pre-thawed Type A Male-donor fresh frozen plasma (FFP) are safe alternatives to universal donor Type AB FFP and have been adopted by a few trauma centers in North America because of shortage of AB FFP supply.[98]

Factor concentrates have been used more in Europe than the USA for trauma resuscitation. This method utilizes prothrombin complex concentrates (PCC) and fibrinogen concentrates to specifically target derangement from trauma (increased fibrinolysis, reduced clot strength and formation). This method has benefits for decreased exposure to allogenic blood and decreased waste.[98] Blind administration of PCC without viscoelastic evidence of reduced thrombin generation might lack benefit and increase risk of thromboembolism. Indeed, evidence suggests that reduced thrombin generation is late phenomenon in ATC.[99]

Platelets

Current best practice in trauma resuscitation suggests benefit to early transfusion of platelets to $> 50 \times 10^9\ l^{-1}$ or $> 100 \times 10^9\ l^{-1}$ in TBI.[76] A study of trauma patients revealed a significant increase in 24-h mortality in patients presenting with platelet hypofunction (20 vs 2.1%).[34] Platelet dysfunction is common with severely injured patients and worsened with concomitant head injury.[100 101] Platelets should be filtered, but not warmed upon administration. One unit of apheresis platelets (or 6 pooled units) should be given with each six units of RBC and six units of FFP. Though not widely available, platelet impedance aggregometry (IA) is a promising point of care technique, to quantify the level of platelet hypofunction after trauma.[102] IA works by measuring impedance across silver-coated copper wires as agonists of platelet aggregation are added. These agonists are collagen, adenosine diphosphate (ADP), arachidonic acid (AA), and thrombin-receptor activating peptide (TRAP).

Fibrinogen and cryoprecipitate

Early use of viscoelastic testing in trauma is an essential component of resuscitation and often reveals decreased clot strength and hyperfibrinolysis in ATC. Fibrinogen is a rapidly depleted clotting factor in trauma and contributes greatly to clot strength and platelet aggregation.[103] Current European guidelines suggest early transfusion of fibrinogen (via fibrinogen concentrates or cryoprecipitate), to maintain concentrations greater than 1.5-2 g L^{-1} in the face of major bleeding.[104] When using cryoprecipitate, the component should be filtered and delivered "cold" using 15-20 single donor units (approximately two units per 10 kg/body weight). For fibrinogen concentrate, 3-4 g are administered early. Cryoprecipitate administration is often significantly delayed in resuscitation owing to long thawing times. The PROMMTT study demonstrated a delay of 2.8 h to first fibrinogen treatment, while the ACIT (Activation Of Coagulation & Inflammation In Trauma, 2014) study revealed that cryoprecipitate was usually given after the first six units of RBC.[97 105] Multiple retrospective studies have demonstrated benefit of early use of fibrinogen. Evidence suggests that fibrinogen supplementation can improve survival and lead to earlier

correction of coagulation.[32 91 106] Currently ongoing, FlinTIC (Fibrinogen in Trauma Induced Coagulopathy) is a prospective, randomized, controlled, multi-centre European study designed to look at the effect of early fibrinogen in trauma patients.[107]

Whole blood

The use of fresh whole blood (FWB) for resuscitation has seen a renewal of interest with the use of 1:1:1 protocols sometimes referred to as reconstituted whole blood (RWB). When measured, RWB (1:1:1) profiles remain significantly anaemic, thrombocytopenic, and coagulopathic compared with whole blood.[108] For this reason, some within the trauma community suggests that RWB is not haemostatic.[96 97] Use of FWB in wartime operations has limited published evidence, but appears to limit the worsening of ATC, while having an acceptable safety profile.[109 110] Its use has been mostly limited to far-forward combat locations in austere environments, with limited capacity for blood banking. Two recent studies have demonstrated feasibility and safety in civilian centres.[111 112]

Correction of hyperfibrinolysis

Correction of hyperfibrinolysis is the final component to effective damage control resuscitation. Hyperfibrinolysis is evidenced on viscoelastic assays, by early breakdown of clotted whole blood. The use of tranexamic acid (TXA) as an antifibrinolytic was studied in the CRASH-2 trial. This study of over 20,000 patients revealed significantly decreased mortality in trauma patients presumed to bleed, without increase in thromboembolic events.[85] Trauma systems can use prehospital providers to provide TXA in the first hour of trauma and is being studied in the STAAMP (Study of Tranexamic Acid during Air Medical Prehospital Transport) trial.[113] Augmentation of mortality benefit is possible with co-administration with cryoprecipitate, as seen in the MATTERs-2 Trial.[114] In a study of 2,540 trauma patient clotting patterns, 46% presented with no evidence of fibrinolysis. “Fibrinolytic shutdown” might have contributed to 22% mortality.[115] The use of TXA is currently based on clinical suspicion of presumed bleeding. Roberts and colleagues[116] recommended that to ensure highest clinical benefit, TXA should not be restricted to only those with “high” risk of bleeding. Based on current evidence, it is recommended that all patients presumed to be at risk for significant bleeding, receive TXA 1 gram loading dose followed by a 1 gram 8-h infusion. Further studies should be performed to identify if patients with fibrinolytic shutdown benefit from TXA.

Conclusion

Acute Traumatic Coagulopathy is caused by endogenous factors, but can be worsened by improper medical management. Drivers of ATC are activation of protein C, disruption of the endothelial glycocalyx, consumption of fibrinogen, and exhaustion/dysfunction of platelets. This results in reduced clot strength, auto-heparinization, and hyperfibrinolysis. Patients presenting with ATC have higher mortality and morbidity. Coordinated medical management of the trauma patient based on the principles of Damage Control Resuscitation reduces mortality. Further investigation with prospective randomized control trials is warranted to elucidate best resuscitation strategies and targeted haemostatic therapies. Acute care trauma anaesthesia is a specialized field of medicine, requiring knowledge of trauma-specific derangements and expertise in rapidly stabilizing the critically injured patient.

Authors’ contributions

Study design/planning: W.S., M.F.P.
Study conduct: W.S., M.F.P.
Data analysis: W.S., M.F.P.
Writing paper: W.S., M.F.P.
Revising paper: all authors

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Declaration of interest

None declared.

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