Review

The acute coagulopathy of trauma shock: Clinical relevance

Daniel Frith\textsuperscript{a}, Karim Brohi\textsuperscript{a,}\textsuperscript{*}

\textsuperscript{a}Trauma Clinical Academic Unit, Barts and the London School of Medicine & Dentistry, Queen Mary University of London, UK

\section*{Article Info}

\textbf{Article history:}
Received 15 October 2009
Accepted 22 October 2009

\textbf{Keywords:}
Trauma
Shock
Coagulopathy
Transfusion
Plasma
Activated Protein C

\section*{Abstract}

Recent observational studies have identified an acute coagulopathy in trauma victims that is present on arrival in the emergency room. It has been associated with a four-fold increase in mortality and increased incidence of organ failure. Conventional trauma resuscitation and transfusion protocols are designed for dilutional coagulopathy and appear inadequate in the management of acute traumatic coagulopathy and massive transfusion.

Acute Coagulopathy of Trauma Shock (ACoTS) is caused by a combination of tissue injury and shock, and may occur without significant fluid administration, clotting factor depletion or hypothermia. The mechanism through which acute coagulopathy develops is unclear but activation of the protein C pathway has been implicated.

Standard coagulation tests do not identify cases in a timely fashion and ACoTS should be suspected in any trauma patient with a significant magnitude of injury and shock, as evidenced by an abnormal admission base deficit on blood gas. Development of point of care coagulometers and whole blood coagulation analysers, such as rotational thromboelastometry, may enable earlier laboratory identification of this group. Retrospective studies performed by the American military indicate that resuscitation of severely injured patients with higher ratios of plasma given early may improve outcome and reduce overall blood product use. The place of adjunctive pharmaceutical agents within this strategy remains unclear.

There is an acute coagulopathy associated with trauma and shock that is an independent predictor of outcomes. Delineation of this entity, with directed management protocols should lead to a reduction in avoidable deaths from haemorrhage after trauma.

© 2009 Royal College of Surgeons of Edinburgh (Scottish charity number SC005317) and Royal College of Surgeons in Ireland. Published by Elsevier Ltd. All rights reserved.

\section*{Introduction}

Trauma is a leading cause of death and disability worldwide.\textsuperscript{1} This is reflected in UK mortality statistics and in 2006 over 1500 people died as a result of trauma in Scotland alone.\textsuperscript{2} Haemorrhage accounts for approximately 40% of all trauma deaths and is the leading cause of preventable death.\textsuperscript{3,4} Where death is not rapid due to exsanguination, prolonged shock increases the incidence of multiple organ failure and late mortality.\textsuperscript{5}
Derangements of normal blood clotting after trauma results in difficult haemorrhage control, increases transfusion requirements and worsens mortality.6 Recent observational studies have identified an acute coagulopathy associated with trauma and shock that is present on arrival in the emergency room. Conventional trauma resuscitation protocols are ineffective for treating patients with this condition. This review examines the apparent causes of acute coagulopathy of trauma-shock (ACoTS) in order to assist clinicians identify patients at high risk. Management strategies are discussed with a focus on how to tailor resuscitation protocols to combat it.

Traditional understanding of post-traumatic coagulopathy

Coagulopathy associated with trauma has been recognised for decades and is a constituent of the “triad of death”, together with hypothermia and acidemia. Classically it has been understood as due to loss, dilution or dysfunction of the coagulation proteases. Loss is explained as being due to bleeding or consumption, dilution from fluid administration and massive transfusion, while protease dysfunction results from hypothermia and the effect of acidemia on enzyme function. Trauma patients with the combination of an injury severity score (ISS) greater than 25, pH below 7.10, temperature less than 34°C, and systolic blood pressure less than 70 mmHg have a 98% likelihood of developing a life threatening coagulopathy.7

This traditional description of traumatic coagulopathy depicts it as developing late after injury and as a consequence of continued haemorrhage and subsequent medical therapy (intravenous fluids and massive blood transfusion). Therapeutic protocols for massive transfusion manage coagulopathy appearing late in the clinical course, and fresh frozen plasma (FFP), cryoprecipitate and platelets are administered only after a number of units of packed red blood cells (PRBC), or after the results of laboratory coagulation tests become available.

Acute coagulopathy of trauma-shock

However, in the past 5 years several research studies have demonstrated that some trauma patients arrive in the emergency department with an established coagulopathy. We first reported the existence of an acute coagulopathy of trauma in a retrospective study of the admission coagulation results of 1088 trauma patients transferred to The Royal London Hospital by air ambulance.6 24% arrived in the emergency department with a clinically significant coagulopathy and they were four times more likely to die than those presenting with normal clotting parameters. Subsequent studies performed by independent research groups on a total of over 20,000 patients have confirmed the existence of this early coagulopathy.9–12

All these studies report a strong association between acute coagulopathy and mortality and identified it as an independent risk factor for death.9 It has also been associated with longer intensive care and hospital stays. Patients are more likely to develop acute renal injury12 and multiple organ failure,10 have fewer ventilator-free days10,12 and there is a trend towards an increased incidence of acute lung injury.10 In each study the median time from injury to emergency department admission was short, minimal fluids were administered in the prehospital phase, and patients were not hypothermic.

Factors influencing the acute coagulopathy of trauma-shock

Injury severity is closely associated with the degree of acute coagulopathy seen after trauma. In the London study only 10.8% of patients with an ISS of 15 or below had a coagulopathy compared with 33.1% of those with an ISS over 15.2 This figure increased to 61.7% for those with an ISS over 45. In the larger German study a coagulopathy was evident in 26% of patients with an ISS 16–24, in 42% of patients with an ISS 25–49, and in 70% of patients with an ISS >50, respectively.10 However, not all patients who are severely injured present with a coagulopathy. Tissue trauma alone is not sufficient to produce a coagulopathy.

Shock with tissue hypoperfusion is a strong independent risk factor for poor outcomes in trauma13–16 and appears to be the driver of ACoTS. One study of acute coagulopathy found that no patient with a normal base deficit had prolonged prothrombin or partial thromboplastin times, regardless of injury severity or the amount of thrombin generated.15 In contrast there was a dose-dependent prolongation of clotting times with increasing systemic hypoperfusion. Only 2% of patients with a base deficit under 6 mmol/l had prolonging clotting times, compared with 20% of patients with a base deficit over 6 mmol/l. Higher injury severity increased the incidence and severity of coagulopathy in shocked patients.

Fibrinolysis is activated early after injury, increases with higher injury severity and is exacerbated by shock.17 However, this does not appear to correspond with a depletion of coagulation factors. Although one study found low fibrinogen levels in coagulopathic patients (median 0.9 g/L),11 other studies of ACoTS have found normal levels of fibrinogen and other clotting proteases.12,17 Thrombin generation, as measured by concentration of prothrombin fragments, rises with increasing injury severity and this is not reduced by either acidosis or hypothermia.17 Of the studies to measure platelets the largest found that only 3% of patients presented with low counts (<100,000 x 10⁶ L⁻¹) and this was not an independent predictor of mortality.9 The other two studies found median platelet counts greater than 100,000 x 10⁶ L⁻¹ in coagulopathic and non-coagulopathic patient groups alike.11,12 Rather than being a consumptive coagulopathy ACoTS is due to systemic anti-coagulation and hyperfibrinolysis.

Fluids administered after traumatic injury are acknowledged to have a detrimental impact on clotting function either due to haemodilution and/or direct impairment of clot formation and strength.18 In our original study there was minimal prehospital fluid administration (median 800 ml, no blood) and we identified no relationship between fluid administration and the incidence of coagulopathy. In the German study there was a wider range of fluid volumes administered prehospital and an increasing incidence of coagulopathy with increasing fluids. However, early coagulopathy also occurred in the absence of large fluid volumes. 275 (10%) patients presented with clotting disorders although...
their prehospital resuscitation was limited to 500 ml. Thirty two patients with coagulopathy received no fluids at all during their prehospital phase of care. Although it may exacerbate clotting impairment, the initiation of an acute traumatic coagulopathy does not depend upon large volumes of fluid resuscitation.

Hypothermia after injury may be caused by a combination of environmental exposure, hypo-metabolic skeletal muscle, and iatrogenic infusion of fluids with a sub-physiological temperature. Clinically significant effects on plasma coagulation and platelet function are seen at temperatures below 34 °C and the mortality from traumatic haemorrhage is markedly increased when core temperatures fall below 32 °C. Although mild hypothermia is common in trauma patients, temperatures below 35 °C on admission are present in less than 9% and this variable alone probably has minimal impact on ACoTS. Patient temperature was either normal or not measured in the currently published reports.

Although trauma combined with shock is consistently associated with an acute coagulopathy, the mechanism through which this develops is uncertain. One of our observational studies identified that as hypoperfusion increases there is a rise in plasma levels of soluble thrombomodulin and a fall in protein C levels. This correlated with the development of acute coagulopathy and suggested that there was activation of protein C. Activated protein C is a natural anticoagulant and in excess consumes plasminogen activator inhibitor (PAI-1). We were able to identify a dose-dependent reduction in PAI-1 as protein C levels reduced and a simultaneous rise in tissue plasminogen activator levels with subsequent hyperfibrinolysis.

Theoretically, tissue hypoperfusion increases the expression of thrombomodulin on endothelium which then complexes with thrombin. This has the dual effect of reducing the amount of thrombin available to produce fibrin and increasing circulating concentrations of anticoagulant activated protein C. Pre-clinical studies are underway in our laboratory to investigate this potential intrinsic mechanism for ACoTS.

**Identifying acute coagulopathy of trauma-shock**

Logically, early identification and treatment of ACoTS should lead to a reduction in mortality and morbidity. However, currently there are no validated tests of coagulation that are rapidly able to identify ACoTS and guide therapy in the emergency department.

The laboratory identification and monitoring of coagulopathy predominantly relies upon in-vitro tests of two artificially segregated components of the ‘clotting cascade’. These tests, the Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) were designed to monitor oral anticoagulant therapy, are performed on platelet-poor plasma at 37 °C and usually require 30–60 minutes to process by conventional methods. For haemorrhaging trauma patients requiring acute interventions, results will not be a contemporary reflection of coagulation function. Point of care coagulometers could be used to expedite the processing time for PT and aPTT but are untested for this purpose.

The ‘clotting cascade’ model of haemostasis has been replaced by a cell-based representation of coagulation that recognises the major contribution of platelets to the clotting process. Routine assay of platelets and fibrinogen provides numerical information regarding absolute amounts of these factors but gives no indication of their functional activity. Recently, there has also been a renewed interest in thrombotic control mechanisms (anticoagulant and fibrinolytic systems) and a new respect for the endothelium as an active driver of these processes. Neither of the conventional tests of clotting makes any assessment of these influential components of haemostasis.

Recognition of the limitations of current laboratory clotting tests has led to interest in a potential role for thromboelastometry in trauma. Although it has been used in clinical practice for many years, only recently has the equipment become rapid and stable enough for its use to be extended into the resuscitation room. The modified rotation thrombelastogram analyser (RoTEM) measures viscoelastic properties of whole blood samples during clot formation and subsequent fibrinolysis. By analysing features of the shape and amplitude of the graph plotted the clinician can make some assessment of platelet and fibrinogen function as well as plasma coagulation proteins. A recent study reported on RoTEM measurements in early traumatic coagulopathy. The study was designed to validate the RoTEM results against the standard tests of coagulopathy and samples drawn on admission were pooled with samples drawn at 6, 12 and 24 h for analysis. While the study showed that thromboelastometry is feasible in early trauma it is difficult to draw further conclusions about the characterisation of acute coagulopathy from these results.

In the absence of rapid and comprehensive emergency room haemostasis testing, it is sensible to expect an acute coagulopathy in trauma patients with systemic hypoperfusion, as demonstrated by hypotension or a base deficit over 6 mmol/l, particularly in combination with a high magnitude of injury.

**Treating the acute coagulopathy of trauma-shock**

Traditional massive transfusion protocols have been designed to manage a late-developing coagulopathy caused by dilution. These protocols do not achieve normal haemostasis in trauma patients requiring a massive transfusion. A recent study from Houston examined the effectiveness of their pre-ICU massive transfusion protocol at correcting coagulopathy in severely injured and shocked trauma victims. Ninety seven patients receiving 10 or more units of packed red blood cells during hospital day 1 had an admission INR of 1.8 ± 0.2. Adherence to their massive transfusion protocol with administration of 5 units of FFP (commenced after the 6th unit of PRBC) together with 12 units of PRBCs failed to correct this coagulopathy despite good management of hypothermia and acidosis. By the time of ICU admission 6.8 ± 0.3 h later, coagulopathy persisted (INR 1.6) and this was identified as an independent predictor of mortality in this cohort.

In the absence of timely and robust tests of coagulation, blood component replacement in severely bleeding patients is usually performed empirically based on the number of units of packed red blood cells given. This is often expressed as
control resuscitation'. This strategy is initiated within the first five minutes of arrival to the emergency department for shocked trauma patients. First, a permissive hypotension strategy is employed, limiting crystalloid resuscitation prior to haemorrhage control. Intravascular volume support is preferentially provided through the administration of plasma and red cells. Plasma is given as early as possible, and some institutions utilise pre-thawed plasma as a primary resuscitation fluid. FFP is given in at least a 1:2 ratio with PRBCs. Platelet replacement should probably begin before the eighth unit of PRBC and cryoprecipitate used to treat a definite fibrinogen deficiency.

Renewed clinical interest in the role of the coagulation system has led to the investigation of pharmaceutical agents that modulate haemostasis for use in trauma care. A possible role for recombinant activated factor VII in blunt and penetrating trauma has been the subject of a Phase II multicentre, multinational prospective randomised placebo controlled trial. The need for PRBC transfusion and massive transfusion was significantly reduced in the blunt trauma group but not in the penetrating trauma group. There was no difference in mortality noted between the study group and the control. A phase III trial with earlier administration of this agent has recently been halted due to significantly lower than expected mortality across the study. This may in part have been due to the adoption of the newer resuscitation strategies described above.

Antifibrinolytic drugs (aprotinin, tranexamic acid, and epsilon aminocaproic acid) have been used successfully after major surgery to reduce transfusion requirements and reoperation for bleeding. A large randomized trial (CRASH-2) is currently underway and aims to assess the effects of tranexamic acid in patients with or at risk for significant bleeding with trauma. Currently it is not possible to definitively recommend any of these pharmaceutical adjuncts as part of standardised protocols, although this may change in the future as the results of these trials are published and better tests of coagulation become available.

Conclusions

The identification of ACoTS has challenged conventional understanding of traumatic coagulopathy. It is present on admission to the emergency department and is independently associated with significantly higher morbidity and mortality. It can occur in the absence of hypothermia or significant fluid administration. Although strongly associated with shock and increasing injury severity, the mechanism through which this entity develops is unclear. Observational data implicates thrombomodulin and protein C within environments of hypoperfusion.

Current difficulties with obtaining rapid and comprehensive assessments of the haemostatic system means clinicians should suspect and empirically treat acute coagulopathy in patients at risk. Early use of plasma and other clotting products can be expected to enable earlier definitive repair and improved outcome. Recognition of this has stimulated revision of massive transfusion protocols. Concurrent development and validation of robust point of care tests of coagulation should permit better tailoring of resuscitation to individual needs.

Clinical and basic science studies are in progress to further elucidate the pathophysiology of ACoTS. Confirmation of an intrinsic mechanism may offer the prospect of a novel pharmaceutical agent to combat it early after injury.

Sources of financial support

None

References
