Trends in Anaesthesia and Critical Care 5 (2015) 23–27

Contents lists available at ScienceDirect

Trends in Anaesthesia and Critical Care

journal homepage: www.elsevier.com/locate/tacc

REVIEW

Coagulation in trauma

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Keywords:
Trauma induced coagulopathy
Hyperfibrinolysis
Massive transfusion
Protein C
Coagulopathy

SUMMARY

Uncontrollable bleeding is the major cause of possible preventable death after traumatic injury. Up to one third of patients admitted to the emergency room will develop the so-called trauma induced coagulopathy (TIC) which has been shown to be associated with massive transfusions, increased morbidity and mortality. Several recent studies contribute to our present understanding of the pathophysiological mechanisms of TIC.

In the literature the lethal triad of trauma (hypothermia, acidosis, and coagulopathy), dilution and hypoperfusion including the role of the protein C pathway activation are well described. Recent studies offer evidence for the mechanisms which induce TIC that include platelet dysfunction, endothelial activation/anticoagulation, hypofibrinogenaemia and hyperfibrinolysis which develop very early after traumatic injury. One of the major limitations of the current literature regarding TIC is that most data presented are associations from observational databases, and only a few prospective observational studies exist and causative aspects are only shown by haemorrhagic shock in animal models.

TIC represents a complex interplay between coagulation, inflammation, and cellular dysfunction (platelets, leukocytes, and endothelium). Mechanisms include anticoagulation by the thrombin-thrombomodulin protein C system, platelet dysfunction and hyperfibrinolysis. The understanding of TIC has improved immensely in recent years but many questions remain that need to be answered by other prospective studies and animal models to further define this complex syndrome.

1. Introduction

Bleeding following major trauma leading to haemorrhagic shock remains one of the major causes of death. The simplistic theory of the so-called “lethal triad” including hypothermia, dilution and acidosis does not explain all the pathophysiological mechanisms which lead to acute hypocoagulability and early hypercoagulability following major trauma. The term “trauma induced coagulopathy” (TIC) was introduced to describe a process that impairs blood coagulation and increases blood loss by a possible dysregulation of the intrinsic coagulation system in trauma patients. The aetiology and mechanism of TIC is complex and has not been fully clarified. In addition, Acute Traumatic Coagulopathy (ATC) is the initial process that leads to TIC. Known factors for ATC are tissue hypoperfusion due to blood loss, major tissue injury, inflammation, cellular dysfunction (including platelet dysfunction), hyperfibrinolysis, fibrinogen consumption and anticoagulation. All these aspects are associated with increased transfusion needs, morbidity, length of stay, and negative outcomes. The purpose of this review is to elucidate the different aspects which lead to TIC including animal models that may help better define the different mechanisms involved. We will also briefly review different fluids used during resuscitation, hypothermia, and acidosis that are other critical components of this pathologic process.

2. Acute traumatic coagulopathy and the clinical implication

Acute traumatic coagulopathy (ATC) develops within minutes following trauma. In a French study by Floccard et al.[1] 45 trauma patients had blood samples taken at the scene of their accident and in the emergency room (ER). The laboratory and coagulation test performed showed that in more than 50% of the patients an abnormal coagulation status could be found within 25 min after injury. Carrol et al.[2] measured TEGs (thromboelastography) in 160 patients where blood was also taken at the scene and could also show that TEGs were partially abnormal. These two studies indicate

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http://dx.doi.org/10.1016/j.tacc.2014.10.006
2210-8440/

that patients will have ATC when arriving in the ER. Severe tissue injury combined with hypoperfusion could be the factors implicated in ATC. In a study including 5000 patients admitted to trauma centres Frith et al.[3] reported that neither variable alone independent of their severity was associated with clinical coagulopathy. Increased bleeding relevant prolongations of the prothrombin time were found in combination of a high ISS and acidosis as defined as a base deficiency. A study of 450 patients injured in combat by explosions or gunshots were similar regarding their demographic data (age, GCS, ISS, body temperature, haemoglobin levels, SBP and mortality).[4] Patients implicated in explosions presented more tachycardia, had worse base deficiencies, higher INRs and a higher incidence of coagulopathies compared to the gunshot patients. This suggests that shock is the main driver for ATC but tissue injury is necessary in addition. Other factors leading to TIC are hypothermia, acidosis, and haemodilution which all develop over time due to injury as consequences of bleeding, hypoperfusion, and resuscitation with products that haemodilute patients contribute to the hypocoaguable state. These aspects are discussed later in this article. To date, all studies regarding ATC have confirmed that this condition is associated with higher transfusion needs and also with a fourfold increase in mortality.[5,6] Frith et al.[3] reported that there was a significant and even dose dependent increase in mortality and blood product use in trauma patients for those arriving in the ER with a PT higher than 1.2.[3] A large outcome study with 8724 polytrauma patients performed by Maegele et al. showed that 1/3 of the patients with ATC had multi-organ failure during their hospitalization compared to 10% in the control group.[7] Mechanical ventilation, length of ICU and hospital stay were also longer in patients with ATC compared to the control group with normal coagulation. ATC leads to increased blood loss in these patients and thus early normalization of coagulation should be achieved to improve patients' outcome.

3. Endothelial dysfunction

Under normal conditions the endothelial cells produce or activate anticoagulants which down-regulate thrombin generation, and include thrombomodulin, endothelial protein C, heparin sulfate and chondroitin. Recent findings have shown that high plasma levels of sydecan-1 are present after trauma.[8–10] This proteoglycan is part of the glycocalyx and its liberation into the circulation could lead to an anticoagulating effect by thrombomodulin inhibition of thrombin and heparin sulfate which increases thrombin inhibition by antithrombin III.[11,12] Endogenous heparinization was shown in 5% of the trauma patients by comparing kaolin versus heparinase TEG.[13] The degree of endogenous heparinization correlates with the levels of sydecan-1 indicating that the cause is the destruction of the endothelial glycocalyx.[13] This finding potentially increases vascular permeability, inflammation, and tissue oedema. A study in rats noted that resuscitation with FFP leads to a restoration of the destroyed glycocalyx.[14] These findings confirm the results of other studies[10,15] and are used to argue why FFP should be used in trauma resuscitation. Another study by Sillesen et al.[16] describes an improvement of platelet function, an increase of fibrinogen (max level of 2 g/l is possible as FFP does not contain more fibrinogen) and endothelial activation. Even in a swine model with haemorrhagic shock where FFP versus saline was used to compensate a 40% blood loss, platelet aggregation measured by APD and arachidonic acid as well as TEG results were better in the FFP group. Furthermore a reduction of the endothelial activation as well as reduced platelet dysfunction was suggested by the authors.[16] What all these studies do not take into consideration is the fact that FFP itself is associated with adverse events that include increased infection rates, higher morbidity and mortality, prolonged length of stay in hospital, TRALI and TACO etc. Although arguments in favour of FFP on a cellular basis are interesting but need to be considered in the context of using blood products and their adverse effects, and ~70% of patients receiving FFP will develop adverse effects and complications.

4. Activated protein C

The function of activated protein C (APC) includes anticoagulation and cytoprotection, and is involved in the early phase of injury leading to TIC. Its generation is linked to thrombin formation and thrombomodulin complex which activate protein C via an endothelial protein C receptor. The APC seems to stimulate the antiapoptoic and anti-inflammatory pathway including a reduction in the endothelial permeability. By inactivating factors V and VIII, APC inhibits thrombin generation and has a potential fibrinolytic effect as it inhibits plasminogen activator inhibitor (PAI-1). Due to PAI-1 inhibition, tPA and uPA can continue to promote the generation of plasmin and fibrinolysis. As mentioned earlier, high levels of APC by admission with coagulopathy is an indicator for increased transfusion needs and mortality.[17] In a mouse model the inhibition of the anticoagulant function of APC protected against TIC whereas the inhibition of the cytoprotective and anticoagulant function lead to death.[18] The reduction of coagulation factors activity (FII, FVII, FIX, FX, FXI) has been proven to be dependent on the degree of shock.[19] The only factor independent of the level of shock regarding its loss of activity was factor V. The anticoagulant effect of APC is important regarding TIC but is probably not the only mechanism of procoagulant inactivation.

5. Oxidative modifications

A new theory on the inactivation of coagulation factors was published by Burney et al.[20] They provided evidence that a modification in the fibrin activated C-subdomain is needed for the lateral aggregation of fibrin during its polymerization. This results in inadequate polymerization and thus in a reduced clot strength.[20] This modification is made by oxidative damage which occurs via oxidative stress induced by haemorrhagic shock. Cells releasing reactive oxygen species are platelets, leukocytes, and endothelial cells after injury, inflammatory signal and hypoperfusion as in shock.[21,22] The release of oxygen free radicals seems to have a major influence on coagulation as PAI-1, protein C and thrombomodulin are to be influences by oxidation.[23–26] This phenomenon might thus also have an important influence on the process of TIC.

6. Hyperfibrinolysis

Hyperfibrinolysis is known to be associated with a higher mortality in trauma patients even though only a small subset will present with systemic activation. Its diagnosis is difficult as there are no clear laboratory tests to identify it quickly and to determine the degree of fibrinolysis.[27] Viscoelastic tests such as ROTEM® and TEG are the only devices to rapidly and effectively identify this pathophysiological process[28,29] Raza et al.[30] showed that hyperfibrinolysis was not due to hypothermia or iatrogenic influences, and thus should be considered as a distinct problem that must be identified and treated early as it contributes to TIC. Plasminogen which is needed for hyperfibrinolysis is activated by tPA and uPA and transformed to plasmin. Plasmin cleaves the cross links of the fibrin clot which can be inhibited by PAI-1. PAI-1 inactivates tPA and uPA.[31–33] An excessive increase of tPA without an upregulation of PAI-1 leads to an imbalance resulting in hyperfibrinolysis.[34] Activated protein C inhibits PAI-1 and is thus links the protein C system