Optimising diagnosis and treatment of coagulopathy in severely injured trauma patients
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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
GENERAL INTRODUCTION

Trauma has a profound impact on public health around the world. Yearly approximately 5 million people die due to traumatic injury, which is 1 out of every 3 severely injured patients\(^1\). Therefore, improving survival after trauma is a major challenge in which timely therapy is of great importance. Although increased knowledge about the mechanisms and pathophysiology of traumatic injury to the human body have led to improved trauma care, surgical procedures, and critical care management over the last decades, still a large proportion of patients die after trauma. Better understanding of how the injury and treatment affect the outcome after trauma may result in a decreased mortality. However, in this field there is still a lot of work to do.

In trauma patients, massive haemorrhage is one of the leading causes of mortality. Exsanguination accounts for more than 30% of mortality in trauma patients\(^2\). The main part of the treatment of massive haemorrhage is to stop the bleeding. However, the development of trauma-induced coagulopathy (TIC) hampers this and exacerbates the bleeding. Therefore, treatment of coagulopathy is a cornerstone in achieving haemostasis and in therapy of bleeding trauma patients.

COAGULOPATHY

Coagulopathy is a condition of the blood in which the blood’s ability to coagulate is impaired. However, the term coagulopathy can relate to several divers conditions. Intensivists associate coagulopathy with disseminated intravascular coagulopathy (DIC), which is characterized by an increased tendency of clotting of the blood, also known as hypercoagulopathy, which is thought to contribute to organ failure and late mortality. Trauma surgeons interpret coagulopathy as a diminished clotting function, also known as hypocoagulopathy, which is associated with early mortality. Additionally, several terms in literature are used to refer to the same condition. Terms such as acute traumatic coagulopathy (ATC), early coagulopathy of trauma (ECT), trauma-induced coagulopathy (TIC), and the acute coagulopathy of trauma-shock (ACoTS) are commonly used. Both the various interpretations and terms used for coagulopathy, illustrate the lack of knowledge on the dynamics of the coagulation process in trauma. In this thesis we will further discuss coagulopathy after trauma. The term in this thesis used for coagulopathy is trauma-induced coagulopathy (TIC) and refers to a diminished clotting function, also knowns as a hypocoagulable state, upon arrival at the Emergency Department.
TRAUMA-INDUCED COAGULOPATHY

Almost 25% of the severely injured trauma patients have developed hypocoagulopathy on arrival to the Emergency Department. Compared to trauma patients without coagulopathy, patients with TIC have a fourfold higher risk for mortality. Early mortality is determined by a hypocoagulable state and bleeding to death, whereas late mortality is determined by a hypercoagulable state and the development of multiple organ failure.

The hypocoagulable state increases the risk for bleeding and exacerbates blood loss. This early mortality by haemorrhage is one of the leading causes of death in trauma patients, but it is also the most preventable cause of death. Treatment of coagulopathy is a cornerstone in achieving haemostasis and in therapy of bleeding trauma patients, as controlling the bleeding by a surgical procedure is not possible without a good functioning clotting system. However, overtreatment of TIC may result in a hypercoagulable state, which is associated with the development of multiple organ failure and late mortality. Therefore, to treat TIC adequately, knowledge about the pathophysiology and dynamics of coagulopathy in the course of severe trauma is required.

PATHOGENESIS OF TRAUMA-INDUCED COAGULOPATHY

Conventional theory holds that early TIC was caused by hypothermia, acidosis and dilution, also known as the lethal triad. Hypothermia and acidosis result in the dysfunction of clotting enzymes, whereas administration of resuscitation fluids dilutes the concentration of clotting factors in blood. TIC results in an increased blood loss with exacerbation of hypovolemic shock and concomitant decreased perfusion of organs, which leads to hypothermia, acidosis and subsequently death.

However, nowadays it is suggested that early development of TIC is caused by external factors, like hypothermia, dilution and acidosis, in combination with a response of the body to tissue injury. After tissue injury, endothelial cell activation results in the initiation of the pro-inflammatory response system and the triggering of thrombo-thrombomodulin complexes. These complexes activate protein C, also known as the protein C pathway. Activated protein C inhibits clotting factors V and VIII thereby reducing the clotting function. However, in trauma, the presence of shock and sustained hypoperfusion, causes an increased release of thrombo-thrombomodulin complexes, which results in a widespread protein C activation and an impaired clot formation. Additionally, besides the fact that clotting factor V and VIII are inhibited by activated protein C,
protein C depletes plasminogen inhibitors, including (PAI-1). Normally, plasminogen inhibitors have the function to inhibit the formation of plasminogen in to plasmin. The breakdown of the fibrin network and subsequently the clot is thereby prevented. However, depletion of plasminogen inhibitors by protein C results in an increased clot breakdown, also known as hyperfibrinolysis. This hypocoagulable effect is further enhanced by the release of small molecules of heparin-substances after endothelial damage. Together this aggravates a hypocoagulable state, blood loss and subsequently increases haemorrhagic-related deaths\textsuperscript{12-16}. Figure 1 illustrates the pathogenesis of coagulopathy after trauma.

At the same time, consumption of activated protein C occurs after trauma. This depletion of protein C is a potential mechanism for the development of hypercoagulopathy. Due to depletion of protein C, clotting factor V and VIII and plasminogen inhibitors are no longer inhibited, which may result in a hypercoagulable state. It is suggested that this hypercoagulable state is associated with the formation of micro-thrombi, also known as DIC, and the formation of multiple organ failure after trauma\textsuperscript{17-20}. Also, depletion of protein C leads potentially to an impaired immune response and subsequently a higher risk of infectious diseases\textsuperscript{12-16, 21-23}. In line with this, previous studies reported lower levels of protein C levels in patients with sepsis and ventilator-associated pneumonia in critically ill trauma patients\textsuperscript{14, 24}. This indicates that the immune system and the coagulation system are interlinked and that activation of the immune system is associated with a pro-coagulant effect in trauma patients. However, which mediators are responsible for this, is unknown. Results of previous studies suggest that a prompt release of microparticles, which are vesicles which are shed into the bloodstream by cells under conditions of stress, are associated with both a pro-coagulant and a pro-inflammatory immune responses\textsuperscript{25-29}. However, whether this also applies to trauma patients remains to be determined. Hypo- and hypercoagulopathy after trauma poses a challenge to the trauma team, with the need for awareness and timely treatment of the lethal triad while avoiding unnecessary transfusion. The diagnosis and treatment of TIC is a cornerstone in this process.

**DIAGNOSIS OF TIC**

Early detection and identification of trauma patients with coagulopathy is required to optimise therapy. Activated partial thromboplastin time (aPTT), prothrombin time (PT), the international normalized ratio (INR), platelet count, fibrinogen and d-dimer are conventional clotting tests, which are used frequently in the clinical setting. However, the use of these tests is rather based on tradition than on evidence based medicine supporting the use of these tests in trauma setting. Conventional clotting tests are
FIGURE 1: Pathogenesis of coagulopathy

- Trauma
- Bleeding
- Haemorrhagic shock

- Hypocoagulopathy
  - Inhibition FVa and FVIII
  - Depletion of PAI-1

- Hyperfibrinolysis

- Activation Protein C
- Extracellular histones
  - Consumption of clotting factors
  - Hypothermia
  - Acidosis
  - Hypoperfusion

- Thrombin-thrombomodulin complexes

- Depletion Protein C
- Hypercoagulopathy
- Venous trombo-embolic events
- MOF
very time-consuming as results become available after at least 40-60 minutes. Also, these tests reflect only a part of the clotting profile. Thereby, these tests have minimal impact on transfusion practice in bleeding trauma patients. Although these tests are commonly used to evaluate and to predict bleeding, these tests are originally designed to diagnose coagulation disorders and to evaluate anticoagulant medication. Therefore, transfusion practice is currently more an empiric procedure than based upon adequate clotting tests. This is alarming, as conventional clotting tests do not allow for correct diagnosis of TIC and hence no targeted therapy is possible. In conclusion, no adequate diagnostic and monitoring tools for coagulopathy in trauma patients are available nowadays.

Viscoelastic Heamostatic Assays (VHA), like thromboelastometry (ROTEM®) and thromboelastography (TEG®), are rapid tests which reflect the whole coagulation status. Within 5-10 minutes a first impression of the clotting function is visualized. VHA tests provide an impression for global haemostasis, including the measurement of the total coagulation process from clot formation until clot breakdown. Therefore the use of these VHA assays may be a valuable alternative for diagnosing and monitoring of the effectivity of treatment of TIC in bleeding trauma patients. However, clear reference values for coagulopathy in trauma patients still need to be determined, as the manufacturer has provided only general reference values. Furthermore, it is unknown what the monitoring capacity of these VHA assays is and whether implementation of these tests results in optimization of transfusion by avoiding transfusion unnecessary blood products and pro-coagulants. Additionally, it remains to be determined whether VHA assays can be used to provide targeted transfusion in trauma patients and what the triggers and targets are for transfusion. Currently, the suspicion of bleeding, hypovolemia and the haemoglobin level are frequently used as triggers for transfusion, however it is unknown whether these factors predict bleeding adequately and are able to use as a transfusion target. Therefore, adequate and rapid diagnostic tools for coagulopathy are required to optimise and monitor treatment of coagulopathic trauma patients.

TREATMENT OF TIC

Over the last decades, research efforts in the field of transfusion practice in trauma patients have been directed towards treatment of the principle drivers of the lethal triad, including hypothermia, acidosis and coagulopathy. Therefore, supportive care in trauma consists of prevention of hypothermia and the administration of fewer fluids. From this point of view, prevention of hypothermia and a restricted fluid policy have become part of standard trauma care. Additionally, transfusion practice has evolved from
administration of red blood cells (RBCs) towards earlier administration of fresh frozen plasma (FFPs) and platelets (PLTs) to red blood cells (RBCs). A RBC:FFP:platelet ratio of 1:1:1 is suggested to be the closest approximation of whole blood and contributes to the achievement of haemostasis thereby decreasing mortality.

In order to obtain a balanced ratio of blood products, massive transfusion protocols (MTPs) are increasingly being used in trauma care. MTPs attempt to provide rapid and standardized issuing of blood products in a 1:1:1 ratio and aim to reduce time-to-transfusion by keeping pre-thawed plasma available. However, evidence for a beneficial effect of implementation of the MTP on obtaining a balanced transfusion ratio, coagulation profiles and overall survival is still lacking. Furthermore, it is unclear whether implementation of an MTP results in an increased incidence of overtransfusion of blood products. Overtransfusion is still a frequently observed phenomenon and is associated with adverse events like sepsis and multiple organ failure.

Alternative transfusion strategies with early balanced resuscitation in order to control TIC and to decrease traumatic bleeding while avoiding unnecessary transfusion are therefore required. An alternative to empiric use of ratios may be transfusion practice
AIM AND OUTLINE OF THE THESIS

This thesis focuses on knowledge gaps in the field of diagnosis and treatment of TIC in severely injured trauma patients. In order to explore potential diagnostic tools for TIC and to investigate potential strategies to optimise treatment of TIC, the Academic Medical Center of Amsterdam has been participating in the International Trauma Research Network (INTRN) since 2012. The INTRN is a consortium of 6 European Level-1 trauma centres, which received funding from the European Union Framework Programme 7 (FP7) to perform research in the field of coagulopathy after trauma. This thesis is partly established by collaboration with INTRN and by using a large database of trauma patients. The aim of this thesis is to evaluate diagnostic tools for TIC and to investigate which transfusion strategy is associated with the best outcome after trauma. The first part of this thesis focuses on optimising diagnosis of TIC, whereas the second part of this thesis focuses on optimising treatment of TIC.

PART 1 DIAGNOSIS OF COAGULOPATHY

- **Chapter 1** provides a narrative review of the utility of ROTEM® and TEG® to detect coagulopathy in critically ill non-bleeding patients.
- **Chapter 2** assesses the predictive value of hypercoagulopathy detected by ROTEM® for the development of multiple organ failure.
- **Chapter 3** determines the association between the haemoglobin level and the neurologic outcome of patients after traumatic brain injury.
- **Chapter 4** investigates the role of microparticles in mediating the immune response following trauma.

TREATMENT OF COAGULOPATHY

- **Chapter 5** gives a systematic overview of the risk factors related to coagulopathy and transfusion practice for adverse outcome after major trauma.
• Chapter 6 emphasizes the detrimental effect of accidental hypothermia on mortality in coagulopathic trauma patients at admittance to the intensive care unit.
• Chapter 7 studies the effect of the introduction of an MTP on the use of blood products and transfusion ratios.
• Chapter 8 systematically determines alternatives for the transfusion of AB-plasma in massively bleeding patients.
• Chapter 9 investigates which transfusion strategy is associated with best outcome in bleeding trauma patients.
• Chapter 10 determines the response of ROTEM® to transfusion practice in bleeding trauma patients.
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massive transfusion or massive confusion?