Optimising diagnosis and treatment of coagulopathy in severely injured trauma patients
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SUMMARY AND FUTURE PERSPECTIVES
SUMMARY

In trauma patients, massive haemorrhage is the leading cause of mortality. Exsanguination accounts for more than 30% of mortality in trauma patients\(^1\). 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 TIC is a cornerstone in achieving haemostasis and the therapy of bleeding trauma patients. Controlling the bleeding by a surgical procedure is not possible without a good functioning clotting system. However, adequate diagnosis and treatment of TIC remain major challenges to physicians. Therefore, more knowledge about coagulopathy and bleeding in trauma patients is required to improve outcome. For example, identifying trauma patients who are at high risk for coagulopathy might result in an increased survival. The first important question is: how are we able to diagnose TIC rapidly and accurately and how do we treat trauma patients with a diminished clotting ability? Nowadays, we use conventional clotting tests to diagnose coagulopathy, however these tests are time-consuming and useless in the treatment of coagulopathy\(^2-5\). Results become available when the bleeding trauma patient is already exsanguinated or transferred to the operating theatre or the intensive care unit. Currently, there is no accurate diagnostic and monitoring tool for TIC. Transfusion of blood products is therefore empirical rather than based upon precise laboratory tests. Viscoelastic Hemostatic Assays (VHAs) have shown promising results in their ability to identify TIC in trauma patients\(^6-10\). However, these tests have not yet been validated in trauma patients and it is unknown which threshold values are applicable to trauma patients. Furthermore, if a coagulopathic trauma patient has been identified, it is undetermined which transfusion therapy is associated with normalization of the clotting system and the best outcome.

While TIC needs prompt treatment, overtransfusion should be avoided, as there is a clear correlation between blood transfusion and adverse outcome. There is a knowledge gap also in determining who does NOT need aggressive correction of TIC with transfusion therapy. In treating trauma patients, the second question is: how are we able to succeed in achieving timely transfusion, while avoiding unnecessary transfusion of blood product?

This thesis focussed on some of these specific knowledge gaps in the field of diagnosis and treatment of TIC in severely injured trauma patients. The first part of thesis discussed the diagnosis and the second part the treatment of TIC.
SUMMARY OF RESULTS

PART 1

Diagnosis of TIC

Conventional clotting tests reflect only a part of the coagulation status and are time-consuming. Therefore alternatives for diagnosing coagulopathy in trauma patients are warranted. Thromboelastometry (ROTEM®) and thromboelastography (TEG®) are point-of-care devices, which are able to detect the coagulation status throughout the process of clot formation until clot breakdown. However, whether these tools are also valuable in the prediction of outcome remains to be determined. An increasing amount of attention for VHAs is being observed, although studies in this field are limited. In the narrative review in Chapter 1 an overview is given of the utility of the ROTEM® and TEG® to detect coagulopathy in critically ill non-bleeding patients. In sepsis patients it appeared that hypocoagulopathy was associated with multiple organ failure, also known as disseminated intravascular coagulation (DIC). However, in contrast to these findings, in trauma patients a hypercoagulable state as measured by VHA predicted the development of thrombo-embolic events, although not all studies confirmed this finding. Due to heterogeneity of study designs and control groups, lack of reference standards and variability of chosen endpoints, it was not possible to draw definite conclusions.

Chapter 2 aimed to further determine the association between coagulopathy and multiple organ failure. This chapter focused on the predictive ability of hypercoagulopathy detected by ROTEM® for the development of multiple organ failure. Multiple organ failure is the main cause of late mortality among trauma patients. Early detection of multiple organ failure may provide opportunities for prevention of MOF, e.g. by interfering with coagulation status. However, in contrast to the hypothesis of this study, hypocoagulopathy instead of hypercoagulopathy on arrival to the Emergency Department, was associated with the development of MOF. I suspect that a hypocoagulable state on admission transfers towards a hypercoagulable state later during hospital stay, which may predispose to MOF. The consumption of protein C may be paramount in this process. This is further elaborated in chapter 5, in which we reviewed risk factors for MOF in trauma. This will be discussed under the heading treatment of TIC.

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. Additionally,
these triggers may differ between specific patient populations. For example, in patients suffering from traumatic brain injury (TBI), it was shown that the injured brain may not tolerate lower haemoglobin (Hb) levels in an effort to maintain adequate cerebral oxygenation in order to prevent secondary ischemic injury to neuronal tissue. At the same time, there is an association between transfusion and adverse outcome of TBI. Therefore, early diagnosis and treatment of coagulopathy and bleeding may improve survival in these patients. However, the effect of a low Hb level on the neurologic outcome is less well determined. Therefore, the association between a low Hb level and neurologic outcome in critically ill traumatic brain injury patients was determined in Chapter 3. As hypothesized, a low Hb level was associated with a poor neurologic outcome in traumatic brain injury patients. In particular, multi-traumatized TBI patients were at high risk for a reduced neurologic recovery. Multi-traumatized TBI patients received more blood products, which suggest that blood loss was more pronounced in multi-traumatized TBI patients, which may result in a reduced cerebral oxygenation and a poorer neurologic outcome. Large randomized controlled trials in TBI patients are required to further investigate the association between low Hb levels and neurologic outcome and to investigate whether maintenance of higher Hb levels improve functional outcome in TBI patients.

Previous studies have reported that microparticles (MPs) have an important role in activating the coagulation system after trauma. As the coagulation system and the immune system are integrated, it is likely that MPs could also mediate the immune response after trauma. Therefore, the role of endogenous MPs in mediating the immune response after trauma was investigated in Chapter 4. Results indicated that severely injured trauma patients have a reduced immune response, which was strongly associated with a decreased number of circulating endogenous MPs. In particular, MPs derived from platelets, were able to drive the synthesis of proinflammatory cytokines, thereby contributing to host response and abrogating immunoparalysis. This begs the question as to whether MPs may be used in future studies as an interventional target. Furthermore, given the association between MPs and the coagulation ability, the question is whether transfusion with blood products containing exogenous MPs contribute to the improvement of the inflammatory status and improve TIC.

PART 2

Treatment of TIC

Elaborating on the findings of Chapter 1 and 2, in which the role of TIC as a driver of early and late outcome of trauma was identified, risk factors associated with TIC and transfusion practice for the development of multiple organ failure after trauma were
assessed in Chapter 5. According to the results of Chapter 2, not hypercoagulopathy but hypocoagulopathy on arrival to the Emergency Department was found to be associated with the development of multiple organ failure. We hypothesized that later during hospital stay, the coagulation profile shifts from a hypocoagulable state towards a hypercoagulable state, which may predispose to multiple organ failure. The consumption of activated protein C results in a decreased inhibition of clotting factor V and VIII, causing a hypercoagulable state. However, future studies are required to confirm this hypothesis. Additionally, risk factors related to transfusion practice for multiple organ failure were determined. The administration of crystalloids, transfusion of red blood cells and a prolonged storage time of red blood cells seemed to increase the incidence of multiple organ failure. Procoagulant therapy was not identified as a risk factor, which indicates that procoagulant therapy has an acceptable safety profile and may be integrated in transfusion practice in order to limit blood loss and transfusion of unnecessary blood products.

Although emphasis has been on transfusion therapy in trauma, the impact of accidental hypothermia on mortality is also high. This may be related to the lethal triad, which include hypothermia, acidosis and coagulopathy. In Chapter 6, the effect of hypothermia upon arrival to the Intensive Care Unit on mortality was assessed. Hypothermia occurred in more than 30% of the patients admitted to an Intensive Care Unit and was identified as an independent predictor for early and late mortality. Other risk factors identified for late mortality include coagulopathy, a high injury severity score, traumatic brain injury and an advanced age.

Massive Transfusion Protocols (MTPs) have been institutionalized in order to provide rapid treatment with plasma. As part of these MTPs, plasma is kept thawed for this purpose. In Chapter 7 we demonstrated that a hospital-wide introduction of an MTP ensures a well-balanced transfusion ratio of red blood cells, plasma and platelets of 1:1:1. However, the group transfused with a balanced transfusion ratio received more blood products, which might be a disadvantage, as transfusion of blood products is also associated with adverse outcomes including infections, acute respiratory distress syndrome and the development of multiple organ failure. Another important finding of the study was that an MTP comes at the cost of an increased waste of fresh frozen plasma, which is caused by keeping pre-thawed plasma available. The waste of blood products was lowered after extending the duration of storage time from 3 to 5 days after thawing.

As a consequence of early plasma transfusion/use of MTP, the use of AB plasma as the universal donor of plasma has been increased. AB plasma does not contain
anti-A and anti-B antibodies and is thought to be safe to administer prior to cross matching. However, blood type AB is less common than other blood types. Also, in the Netherlands, there is a policy of limiting donation of plasma to males, as transfusion of female plasma is associated with the occurrence of transfusion-related acute lung injury. Therefore, blood banks are running out of their AB plasma supplies and call for alternatives. Chapter 8 systematically reviews papers that have examined alternatives for transfusion of AB plasma in massively bleeding patients. The findings of this study suggest that additional research is required as studies in this field are limited. In the meantime, it is recommended to transfuse type-specific plasma. However, in an emergency release setting, when type specific plasma is too time-consuming and AB plasma is not available, A plasma seems to be the best alternative.

In addition to the ratio of blood products, pro-coagulant therapy such as fibrinogen containing products and anti-fibrinolytic therapy such as tranexamic acid (TXA) are increasingly being used during trauma resuscitation. However, until now, no studies have reported the effect of a balanced transfusion ratio in combination with the administration of TXA and fibrinogen products on TIC and mortality. Therefore, the aim of Chapter 9 was to investigate the effect of transfusion ratios, TXA and fibrinogen products on the number of patients requiring massive transfusions (≥10 RBCs in 24 hours) and overall survival in bleeding trauma patients, in a combined model. The second aim was to evaluate which transfusion strategy was associated with correction of TIC, as measured by an elevated INR. We observed that TXA and a high platelet to RBC ratio were associated with an increased number of patients alive and free of massive transfusion. Blood product ratio, TXA and fibrinogen products did not correct coagulopathy as defined by a prolonged INR. Fibrinogen products did not affect outcome, however under-dosing may have influenced the outcome. Of note, the effect of plasma was less apparent. These findings may offer guidance for designing a randomized controlled trial, in which the effect of the addition of TXA and fibrinogen products to a balanced resuscitation will be investigated.

Monitoring of the effect of therapy on TIC is vital in order to treat TIC but avoid overtransfusion. However, the response of ROTEM® to transfusion practice is largely unknown. Therefore, Chapter 10 determined which transfusion strategy was associated with normalization of deranged VHA profiles measured by ROTEM®. The findings of this study indicated that administration of a high ratio of platelets to RBCs was most effective in improving clot formation. The beneficial effect of platelets on the coagulation system may consist of stabilizing of the endothelial cells and aggregation and adhesion of platelets for clot formation. Additionally, platelets provide an efficient surface for accumulation of clotting enzyme complexes. A beneficial effect on normalization of
deranged ROTEM® parameters of clotting was also observed for a high plasma to RBC ratio, however less pronounced. This is surprising, as previous studies including the PROPPR trial, reported a beneficial effect of plasma on the coagulation profile. A possible explanation might be that plasma also contains anticoagulant proteins, which may hamper any potential pro-coagulable effect of plasma. Furthermore, we found differential effects in various patient populations. This suggests that a more personalized treatment is associated with improved coagulation profiles. Thereby, this study is the first attempt towards personalization of transfusion therapy. In theory, such an approach would result in transfusion in those who need it and no transfusion in those who do not, thereby decreasing amounts of unnecessary transfusion with improved outcome and less waste. However, future studies are required to determine whether a targeted, personalized transfusion therapy results in improved outcome and more efficient resuscitation.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Diagnosis of TIC
Prompt and adequate identifying of patients with a high bleeding risk prevents massive blood loss and subsequently haemorrhagic shock-related death. Although conventional clotting tests, like activated partial thromboplastin time (aPTT), prothrombin time (PT), the international normalized ratio (INR), platelet count, fibrinogen and d-dimer are frequently used, these tests are useless in guiding transfusion.

These conventional tests are time-consuming and not adequate in identifying patients with TIC. The impact of these tests on transfusion practice is therefore limited. Until now, transfusion practice has been guided by either empirical ratios or by clinical judgement. This is a major problem, leaving the trauma team at a loss of how to monitor major bleeding. Point-of-care diagnostics like VHA assays may be a valuable alternative for conventional clotting test. However, a recent meta-analysis stated that due to a lack of data, VHA guided treatment should be done in research settings only. Despite these limitations, VHAs like ROTEM® and TEG® are increasingly being used in daily practice and in different patient populations, including trauma patients, without Level-1 evidence. This is alarming, as reference values are lacking and VHAs are not actually validated in trauma patients. More research is required to provide definite recommendations in this field. Furthermore, although the principles of ROTEM® and TEG® are similar, interpretation of the two tests are not interchangeable. Only a small number of studies have compared both tests and the majority of these studies were not performed in trauma patients. Therefore, future studies are required to investigate the comparability of ROTEM® and TEG® in trauma patients.
As part of INTRN and the Activation of Coagulation and Inflammation in Trauma study (ACIT, UKCRN ID: 5637), and by using a large database of trauma patients, this thesis focussed on some of the specific knowledge gaps in the field of diagnosis and treatment of TIC in severely injured trauma patients. This thesis showed that VHAs are promising tools for diagnosis and monitoring of TIC in trauma patients on account of their ability to reflect the whole coagulation profile, from clot formation until clot breakdown. Furthermore, these test accurately and rapidly identify coagulopathy in trauma patients. Results of this thesis pave the way for a trial which will investigate monitoring of TIC with VHAs.

Therefore, these tests are useful for guidance of transfusion practice. These assays make it feasible to shift from a one-size-fits-all empirical treatment towards a tailor made treatment. Currently, a randomized controlled trial, named the Targeted Action for Curing Trauma Induced Coagulopathy, will compare empirical administration of blood product ratios with patient-matched targeted transfusion policy guided by VHAs. This will be the first randomized controlled trial to compare the effectiveness of different transfusion practices across Europe. Based upon the results of this trial, universal guidelines will be delivered for how coagulopathy should be monitored and treated in trauma patients.

Treatment of TIC
Throughout the last decades, an increasing number of studies have investigated transfusion practice in trauma patients. However, mortality associated with massive blood loss is still high. In order to reduce haemorrhagic deaths in severely injured trauma patients, it is important to treat TIC. Various actions have been implemented to prevent and treat TIC. However, which transfusion strategy is associated with best outcome in trauma patients, is still unknown.

The introduction of a massive transfusion protocol based on an empirical ratio approach is an adequate way to achieve transfusion of blood products in a 1:1:1 ratio. However, although time to transfusion is reduced by keeping pre-thawed plasma available, clear evidence for the beneficial effect of the implementation of a balanced transfusion ratio on the correction of TIC and mortality is still lacking. In particular in the context of pro-coagulant and anti-fibrinolytic agents, which are increasingly being used. This thesis showed that pro-coagulant and anti-fibrinolytic agents have a considerable effect on coagulopathy and may to some extent be superior to ratio of blood products in terms of correction of coagulopathy. However, although promising, beneficial effects of these agents have been reported in only a small number of studies and the majority of these studies are conflicting. Furthermore, across the globe, a large variation in transfusion
strategies exists. Studies in hospitals in the United States suggest that pro-coagulant and anti-fibrinolytic agents are given to a minority of patients\textsuperscript{11, 13}, whereas in European hospitals these agents are widely used and are integrated in European guidelines\textsuperscript{14, 15}. Also, the effect of pro-coagulant agents on the occurrence of thromboembolic events is still poorly studied.

Another downside of the implementation of empirical massive transfusion protocols and the administration of blood products in a balanced transfusion ratio, is the waste of pre-thawed plasma, which is remarkably high. Alternatives like freeze dried plasma may decrease the waste of pre-thawed plasma units. However, there is limited experience with free dried plasma in clinical settings.

A better alternative might be personalized transfusion of blood products and pro-coagulant agents by monitoring the coagulation profile by VHAs, thereby avoiding unnecessary transfusion of blood products and pro-coagulant agents. Therefore, we have tried to investigate the response of VHA assays to transfusion of blood products and pro-coagulant agents. Our data suggest that administration of a high ratio of platelets to RBCs has a more profound effect on improving clot formation than a high plasma to RBC ratio. This is innovative as previous studies reported that in particular transfusion of a high ratio of plasma was associated with an improved outcome in critically injured trauma patients. Also, our data suggest that a personalized therapy may improve the coagulation profile and outcome of trauma patients as the response of VHAs to therapy differed between specific patient populations. However, future randomized controlled transfusion trials are required to test whether personalised transfusion may improve outcome after trauma. Currently, a transfusion trial is being conducted, which will compare existing transfusion practice with a targeted treatment of TIC by using ROTEM\textsuperscript{®} and TEG\textsuperscript{®}. This Targeted Action for Curing Trauma Induced Coagulopathy (TACTIC) trial will deliver guidelines and support clinical management of coagulopathic bleeding.
REFERENCES

REFERENCES

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