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Management of critical bleeding in trauma patients: between recommendations and reality

Abstract

Uncontrollable haemorrhage is the most frequent cause of early death in trauma patients. Massive haemorrhage may be exacerbated by coagulopathy early after trauma, and may transit to critical bleeding that does not respond to surgical haemostasis. The treatment strategies should focus on achieving haemostasis as soon as possible and correcting coagulopathy; otherwise efforts at resuscitation are likely to be useless. Rapid control of the source of bleeding with damage control techniques instead of complete repair, interventional radiology especially in abdominal-pelvic trauma, use of blood derived products and haemostatic agents are essential. Rotational thrombelastometry is used to promptly assess coagulation, but when it is not available, routine laboratory-based coagulation tests may be used for assessment of fibrinolysis. Early coagulation support may prevent acquired coagulopathy. The recommendations to avoid critical bleeding are constantly updated but in many situations, due to limited resources they cannot be applied completely. Recognizing the predictors of mortality with early monitoring of prothrombin time, activated partial thromboplastin time, fibrinogen and platelets, target haemostatic therapy with lysine derivates and substituted coagulation factors in order to avoid packed red blood cells and fresh frozen plasma, are of vital importance. Protocol for the treatment of patient with major bleeding will depend on rational strategy which relies on the resources available. Tranexemic acid should be given in massive bleeding, even in the absence of clinically diagnosed hyperfibrinolysis. Fibrinogen and platelets have to be administered in order to provide thrombin formation when hyperfibrinolysis is considered. Bleeding that continues despite fibrin supplementation and adequate number of platelets may be a result of insufficient thrombin formation; in this case prothrombin complex concentrates may be the first line therapy for thrombin deficiency. Strategy in treatment of trauma patients relies on resource availability.

Keywords: trauma, critical bleeding, haemostasis, acquired coagulopathy, hyperfibrinolysis, antifibrinolytic agents, tranexamic acid

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Abbreviations: MOF, multiple organ failure; DCS, damage control surgery; ISS, injury severity score; GSC, glasgow coma scale; PTT, prothrombin time; APTT, activated partial thromboplastin time; PTL, platelets; PRBCS, packed red blood cells; FAST, focused abdominal sonography for trauma; CT, computed tomography; ROTEM, rotational thrombelastometry; FWB, fresh whole blood; TXA, tranexamic acid; TEG, thromboelastography; PCCS, prothrombin complex concentrates; RFVIIA, recombinant-activated factor VII; INR, international normalized ratio

Introduction

Trauma is a serious global health problem and hence it is a particular challenge for those who deal with it. Worldwide, the incidence of trauma mortality continues to rise against the other two leading causes of death. Over the past decades, heart disease declined (2000- 2010) by 31%. Stroke mortality also declined due to reduced stroke incidence observed in sexes, all races and age groups.[1] By 2020, an estimated 8.4 million people will die annually secondary to trauma.[2,3] The concept of trimodal distribution of trauma mortality from the early eighties[4] of the last century has changed in terms of prevalence of early death after injury. There is a decrease of 50% of deaths within 60 min after massive trauma, head injury and respiratory problems, but the majority of deaths still occur within 24 h of injury.[5] Next 30% of deaths occur within the first 24-48 hours after injury as a result of exsanguinations and 20% are late deaths after 48 hours due to multiple organ failure (MOF) and sepsis.[5,6]

Massive haemorrhage is the most frequent cause of early death in trauma patients. A loss of 50% of blood volume without resuscitation is usually fatal and can occur within minutes. Approximately 30 – 50% of deaths that occur immediately and within a few hours (the first 4 hours) after injury are due to acute blood loss and haemorrhagic shock.[7] The lethality of haemorrhage is influenced by the size of the affected vessels and nature of the injury. Massive haemorrhage may be exacerbated by coagulopathies and multi-transfusion syndrome disorders. On average, one of four trauma patients is already coagulopathic upon admission in the trauma center and about one third of transfused patients require massive transfusion. When haemorrhage does not respond to medical or surgical therapy it is considered as uncontrolled bleeding which is a life-threatening condition and is associated with a high mortality rate. Uncontrolled bleeding might be due to acquired coagulopathy as a result of trauma or surgery and due to defect of thrombin generation. By definition, life-threatening haemorrhage is a loss of entire blood volume within 24 hours, loss of 50% blood volume within 3 hours or blood loss exceeding 150 ml/min in 20 min or more.[8,9]

To assess bleeding in trauma is a difficult job since there is no score designed to assess the degree of bleeding, and the estimation is done and based on the mechanism of injury, initial physiology (vital signs), biochemistry (base deficit and lactate) and injuries found on secondary examination. If there is no 'magic measure', and scores are not useful as well as clinical evaluation is complex, then it is quite clear why haemorrhage after traumatic injuries is the biggest dilemma

for treatment, and enormous challenge for the specialists in intensive care, surgery and anesthesiology.

Treatment strategies for patients with trauma bleeding should focus on stopping haemorrhage as quickly as possible in order to prevent multi organ failure and to reduce mortality rate, avoiding massive transfusion and treating coagulopathy. No less important are techniques of damage control surgery (DCS) instead of a complete repair in trauma care. Current and future therapeutic options for the management of traumatic haemorrhage (interventional radiology and use of haemostatic agents) are inseparable part of the overall treatment of these patients.

In general, availability of real trauma data is needed in order to improve outcome in trauma patients. Trauma registry is an excellent tool which is present in all well-organized trauma centers and the registry collects prospective, standardized and anonymous data from all trauma patients and provides many opportunities for determining predictors of death. By analysing various therapeutic options, different outcomes might be found. The role of trauma registry is quick identification of life-threatening conditions by using the most important predictors of outcome and treats them aggressively without causing further harm. Analysis of data of such trauma registry from German Society of Traumatology [10] showed that the most important predictors of the outcome in patients with severe trauma were Injury Severity Score (ISS;), Glasgow Coma Scale (GSC), age, base excess and recently, the initial prothrombin time (PTT) and activated partial thromboplastin time (aPTT), as independent prognostic factors of mortality. Probability of surviving was calculated in selected patients in percentage with the methodology of ISS which estimates the age and the mechanism of injury (blunt and penetrating).

Clinical aspects of trauma bleeding: surgical, non-surgical and critical bleeding

Haemorrhage in trauma patients might become life-threatening when there is surgical and nonsurgical bleeding, as well as when acquired coagulopathy is present. In case of surgical bleeding, an imperative is surgical visualization and surgical control. If this is not properly done, then it might become fatal, with 80% mortality. Rapid control of the source of bleeding is essential in acutely bleeding trauma patients. One of the following methods is used: surgical techniques, packing or tamponading the area of bleeding and ligation of major vessels leading to the bleeding area. Surgery might have catastrophic consequences in some conditions ("open book" fracture of pelvis). For this type of bleeding when surgery can only worsen the situation, angiographic embolization of the vessels leading to the bleeding area is recommended. Early detection of uncontrolled haemorrhage is of vital importance. Unexpected bleeding which does not respond to surgical haemostasis is reserved for nonsurgical bleeding which can be explained as diffuse/microvascular bleeding. This bleeding which occurs simultaneously at different sites is considered to be critical and should alert the surgeon.

Trauma acquired coagulopathy

Despite a successful control of "surgical" bleeding, many trauma patients may exhibit progressive physiological deterioration typically manifested as the vicious cycle of coagulopathy, hypothermia and acidosis. If the "lethal triad" is present, the surgical control might not be successful. This "lethal triad" may resist all efforts of intervention and can contribute to haemorrhagic shock, MOF and death. Once you get in this vicious cycle it is hard to get out! Coagulopathy is the most common bleeding-related cause of mortality in trauma patients. The incidence of coagulation abnormalities, early after trauma, is high and they are independent predictors of mortality. One of 4 trauma patients have coagulopathy at admission.[11] The pathogenesis of coagulopathy is quite complex and multifactorial. Blood cells are lost directly via haemorrhage, and additionally clotting factors and platelets are depleted as a result of vascular injury. Effects of colloid solutions, increased fibrinolysis (hyper fibrinolysis because of reduced fibrin utilization in terms of systemic hypo perfusion), platelets (PTL) malfunction, hypothermia, acidosis, adverse effects of massive transfusion and hypocalcaemia are additional contributors. So far, hyper fibrinolysis is often undiagnosed and not reported, but still the incidence ranges from 2-7 % in trauma patients with high mortality. Hyper fibrinolysis depends on the type of organic trauma and the severity of hypo perfusion.[12] Current concepts of the pathogenesis of coagulopathy after trauma are presented in the extraordinary paper of Hess et al.[13] where it has been confirmed that early acute coagulopathy associated with traumatic injury is recognized as a multi factorial primary condition that results from a combination of bleeding-induced shock, tissue injury- related thrombin-thrombomodulin-complex generation and the activation of anticoagulant and fibrinolytic pathways.[14] Mortality from hyperfibrinolysis is significantly higher in trauma compared to non-trauma patients, and hyperfibrinolysis is an independent factor predicting mortality in trauma patients.[13] The incidence of initial coagulopathy after traumatic haemorrhage is high and is an independent predictive factor for mortality even in the presence of other risk factors.[15]

According to the European guidelines for management of bleeding and coagulopathy following major trauma[16] routine detection of post-traumatic coagulopathy which includes early repeated and combined measurement of PTT, aPTT, fibrinogen and PTL are recommended. Viscoelastic methods may also be performed to help characterize the coagulopathy and in guiding/management of haemostatic therapy. Besides PTT and aPTT, as independent predictors of morbidity and mortality in trauma patients, the importance of other predictors is of particular interest.

Hypothermia as an inseparable part of the "lethal triad" is also a contributing factor to morbidity and mortality. There is a strong correlation between temperature and survival. Temperature less than 350C results in poor prognosis, while temperature less than 320C after the injury gives 100% mortality.[17] Mild hypothermia may lead to reduction of PTL function, while severe hypothermia may reduce the function of clotting factors (enzymatic reaction rates of the coagulation are slowed by hypothermia with prolonging clotting times).[18] Clotting tests performed at 37°C do not reflect the state of the patient, and may therefore be misleading. Finally, acidosis that results from the hypo perfusion that accompanies haemorrhage can also significantly prolong bleeding by decreasing the activity of clotting factors.[19]

To combat severe haemorrhage and prevent the onset of haemorrhagic shock, multiple transfusions of packed red blood cells (PRBCs) were often administered in the past. In patients with massive haemorrhage one third of transfused patients require massive transfusion. According to American College of Surgeons and Advanced Trauma Life Support classification of haemorrhage severity, loss of 50% of blood volume require 4 or more units for 3 hours, while loss of one blood volume means that for 24 hours the patient will receive 10 units.[20,21] This aggressive restoration of blood volume prior to surgical treatment[22,23] may lead to re-bleeding and worsen survival. Administration of blood products may lead to potentially fatal complications. Massive transfusion can itself result in abnormalities of electrolytes, clotting factors, pH and temperature, which can

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cause coagulopathy and irreversible shock.[24] Allogenic transfusion can result in infection, alloimunization and immunosuppression.[25] Uncontrollable haemorrhage when massive transfusions are given can lead to coagulopathy.

Optimal treatment of critical bleeding in trauma

Recommendations for managing bleeding in trauma are constantly upgraded and revised as important new evidence becomes available due to various approaches in treatment and success in the outcome. The new strategies in the management of trauma patients necessitate an interdisciplinary approach, associated with implementation of the organizational structure, team potency, surgical techniques and availability of the resources. However, we do not always have sufficient resources to implement all recommendations, and then it is very important to determine the optimal treatment for critical bleeding in trauma.

The first most important thing is to establish the exact diagnosis and, in addition to clinical examination, to routinely employ imaging techniques. Ultrasound and color Doppler are used to detect blood in the peritoneal cavity, organ disruption and vascular injury. In addition, focused abdominal sonography for trauma (FAST, an acronym that highlights the necessity of rapid performance) is a very important diagnostic test for abdominal and thoracic bleeding. Computed tomography (CT) scan of the whole body is being used increasingly in order to detect damage and to undertake subsequent treatment decisions.

If we accept that massive haemorrhage in trauma patients consists of a combination of bleeding from vessels requiring surgical treatment and diffuse coagulopathic bleeding, then it is well-recognized that early intervention is important in reducing early and late mortality and morbidity in trauma patients. To avoid the complications of haemorrhage and to prevent the presence of critical bleeding, as well as risks associated with blood transfusion, it is essential to rapidly achieve haemostasis and correct coagulopathy. The "tap must be turned off"; otherwise, efforts at resuscitation are likely to be useless. This generally involves surgery, notably DCS,[26] and administration of clotting factors.

Damage control surgery which is in fact resuscitative surgery is recommended against the traditional approach. Treatment of multiple trauma in the past involved an urgent treatment of all injuries with complex and prolonged interventions. Often the patient survived the initial operation, but subsequently died from continued haemorrhage or MOF. The new approach of treating with shortened surgical interventions involves series of short operations (<60 min), performed hours or days apart in accordance with physiological tolerance. Damage control surgery can decrease surgical time and increase salvage rates in patients who previously would have died. Damage control resuscitation strategies have demonstrated improved survival, hemostasis, and smaller number of deaths from exsanguinations, suggesting that haemorrhage control should be an additional endpoint in resuscitation.[27] In some cases of polytrauma, especially fractures of the pelvic ring, surgery is not always a choice. Interventional radiology for controlling of the bleeding in abdominal-pelvic trauma is a life-saving procedure and might be used,[28] but lack of resources is the main reason why it is used in a very small number of selected patients.

According to the European guidelines,[16] monitoring and coagulation support should start as early as possible. Complete and rapid monitoring of blood coagulation and fibrinolysis using viscoelastic methods may facilitate a more accurate targeting of therapy. Rotational thrombelastometry (ROTEM) provides a means to rapidly assess coagulation in trauma patients, allowing targeted use of blood products, but it cannot be performed in all urgent centers and yet it is not always supported by positive results of its application. Its use in trauma has still to be fully evaluated.[29] Early routine coagulation tests are of particular importance, especially in the first 30 minutes to 1 hour after admission of patients with traumatic haemorrhage. Initial coagulation profile by examining the PTT and aPTT, PTL and fibrinogen as predictors of outcome in these patients may also initiate more aggressive attitude to coagulation support and in that way prevention of acquired coagulopathy. So it is a good clinical practice along with taking blood for biochemical tests to send blood for determination of PTT and aPTT, PTL and fibrinogen.

When we have an actively bleeding trauma patient with an immediate life- threatening injury, it is always problematic to decide what to give, fresh whole blood (FWB), PRBCs , fresh frozen plasma (FFP), cryoprecipitate or PTL. Massive transfusion is very common, and FWB is used to sustain resuscitation when other blood products are unable to be delivered.[30] Despite the known side effects of massive transfusions with FWB, in certain cases, particularly when it comes to injuries combined with massive bleeding, survival for massively transfused trauma patients receiving FWB appears to be similar to patients resuscitated with PTL.[31] These results have been obtained in studies involving the military, but when standard blood products are unavailable, FWB is a feasible alternative. However, prospective trials are necessary before consideration of FWB in the routine management of civilian trauma.

Regarding the use of blood products, there is still a debate about the optimal ratios of various blood products. Based on the battlefield experience, the US Army has instituted a policy of using a 1:1:1 ratio of PRBCs : FFP : PTL for those that are expected to receive more than 10 units PRBCs (massive transfusion). However, till now there are no randomized clinical studies that have conclusively identified the optimal ratios of blood components. Recently, again resuscitation with a 1:1:1 ratio of units of FFP and PTL to PRBCs was well-tolerated and reduced haemorrhagic mortality during resuscitation in the Pragmatic Randomized Optimal Plasma and Platelet Ratios (PROPPR) trial.[32] In an attempt to find a reasonable approach, and taking into account the different massive transfusion protocols, it seems that early start with FFP and PRBCs: FFP in a ratio of 2:1, and administration of 6 units of PTL for every 10 units of PRBC is in accordance with the European guidelines and is acceptable in the routine practice.[33] The amount of plasma that is required will depend on the other blood products, and best monitoring of coagulation, but still no clear consensus on the appropriate dose of FFP exists, especially when ROTEM is not available. In patients with multiple trauma and massive haemorrhagia, PTL are administered with the aim of maintaining the PTL count above 100 × 109/l, as recommended by the guidelines. In order to prevent and treat trauma-induced coagulopathy early coagulation support (ECS) protocol is proposed in order to decrease blood product consumption and 28-day mortality.[34]

Additional options for coagulation support in bleeding trauma are administration of anti-fibrinolytics (lysine derivates, e - aminocaproic acid, tranexamic acid (TXA), and serine protease inhibitor, aprotinin) and substitution of coagulation factors (fibrinogen, recombinant activated factor VII (rFVIIa), prothrombin complex concentrate, desmopressin and antithrombin III). The principal haemostatic agents available for the control of haemostasis and the management of trauma-

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related haemorrhage are antifibrinolytic agents. If possible, anti fibrinolytic therapy should be guided by thromboelastography (TEG) and should be withdrawn once bleeding is under control. Again, when this is not possible, then routine laboratory-based coagulation tests are recommended for administration of anti fibrinolytics in patients with hyperfibrinolysis. Inhibition of fibrinolysis with antifibrinolytics reduces bleeding after tissue injury. According to the new concepts, antifibrinolytics reduce bleeding after extensive tissue injury that occurs with trauma or surgery. Recent studies show that inhibition of fibrinolysis with TXA after major trauma is an important mechanism to reduce mortality.[35] A novel model for antifibrinolytic therapy with TXA has become popular in recent years with very promising results. Tranexamin acid as a primary haemostatic target for management of acquired bleeding is confirmed by few ongoing studies. A crucial aspect of the original idea for the randomised controlled study of an antifibrinolytic agent used in a significant haemorrhage (CRASH2)[36] was to reduce bleeding, an important cause of mortality after trauma, by use of an antifibrinolytic agent. Because tissue injuries in trauma and surgery are similar, researchers hypothesized that TXA could reduce mortality. The effects of early administration of a short course of TXA (loading dose 1 g over 10 minutes followed by infusion of 1 g over 8 h) on the risk of death, vascular occlusive events and the receipt of blood product were assessed. The results showed that TXA reduced the rate of death from bleeding for 1/3, all-cause mortality was significantly reduced and the risk of death due to bleeding was significantly reduced. A further analysis of the CRASH-2 data showed that early treatment (≤1 h from injury) significantly reduced the risk of death due to bleeding. Treatment administered between 1 and 3 h also reduced the risk of death due to bleeding, while treatment given after 3 h seemed to increase the risk of death due to bleeding without increasing the risk of vascular occlusive events. Furthermore, authors recommended the first dose of TXA to be administered at the site of injury. CRASH-2 is an example of the complexity of relations between coagulation, fibrinolysis, inflammation outcomes after tissue injury.[37] Further research regarding trauma and TXA is needed to determine how patient selection and inter current treatment affect safety and efficacy.[38] Till now, there is no evidence on the increased risk in trauma, but CRASH-3 will address the issue of head injury. Tranexemic acid reduces bleeding in surgical patients[39] and this evidence can be used for similar effects in trauma bleeding. Although percentage of reduction in blood loss with TXA differs by type of surgery and timing of administration, the differences are small. A total dose of 1mg appears to be sufficient for most adults and there is no evidence to support usage of higher doses. Minimizing blood loss during a major surgery with anti fibrinolytic agents has also been confirmed in studies where lysine analogues were effective in reducing blood loss during and after surgery and appeared to be free of serious adverse effects.[40] Nowadays, a study is currently recruiting participants for assessing the effect of pre-hospital anti fibrinolytic agents on traumatic coagulopathy and haemorrhage (The PATCH study). The purpose of this research was to determine whether administration of TXA in severely injured adults as soon as g possible would improve their chances of survival and their level of recovery at six months.[41] There are certain views that TXA has an anti-inflammatory effect resulting from fibrinolysis-regulatory mechanism. Having in mind that free plasmin activates PTL, transiently activates/deactivates factor V and factor VIII, and binds to receptors on the endothelium and monocytes[42] initiating inflamatory processes, then if plasmin production is blocked by TXA, PTL, coagulation and inflammation would be less activated.

Prothrombin complex concentrates (PCCs) are able to normalize levels of vitamin K-dependent clotting factors and they are therefore recommended only for emergency reversion of vitamin K-dependent oral anticoagulants.[16] But, PCCs are also able to reestablish haemostasis and may also be used as adjunctive therapy in patients with massive bleeding, which is the case in many European countries. However, further investigation related to therapy for dilution coagulopathy in trauma and surgery is needed.[43] Fibrinogen is the first factor that reaches a critical level in case of bleeding. The role of fibrinogen as a haemostatic agent in management of traumatic haemorrhage is controversial since false positive values immediately after admission of trauma bleeding patients have been found. Due to administration of colloid plasma expanders given early in resuscitation, critical level of fibrinogen is significantly higher than 1 g/L, level that is set theoretically. Thus, it is accepted to start treatment with fibrin concentrate or cryoprecipitate when fibrinogen is less than 1.5-2 g/L.[16]

There were promising results when recombinant-activated factor VII (rFVIIa) came on the scene and evidences of its effectiveness in the treatment of uncontrolled bleeding led to many studies that examined its effect on critical bleeding in traumatic haemorrhage.[44] Animal models have shown that rFVIIa effectively decreases blood loss at trauma[45] and also increased evidence of its efficacy at trauma patients was found.[46,47] In a multicentre, double-blind, prospective, randomized, placebo-controlled trial rFVIIa was shown to be effective and safe in reducing PRBCs transfusion especially in blunt trauma patients, as well as showing a good safety profile[48] when used as an adjunct to trauma care.[49] This does not mean, however, that rFVIIa should be administered to every trauma and surgery patient; optimal patient selection is vital. Although rFVIIa has shown success in reducing haemorrhage in trauma and surgery, there is not sufficient number of randomized controlled trials that will confirm its efficacy and clarify unresolved issues. It is important to determine optimal dosing regimens, optimal time of administration, criteria for patient selection, as well as adverse event profile in order to confirm its effect in improving outcome in trauma patients with uncontrolled haemorrhagia. Such kind of controlled studies will contribute to changing its "off-label" use status to safe and successful use of rFVIIa. However, rFVIIa is a promising agent, particularly when surgical haemostasis is difficult to achieve (e.g. Major blunt trauma)[16] or when conventional therapies are unsuccessful.

Treatment of critical bleeding after trauma between recommendations and reality

Not always recommendations are in use in the real word in trauma and urgent centers. Very often those who care of bleeding trauma patients do not have available resources to follow all the recommendations. In such cases some of the following procedures might be taken into consideration. Monitoring of coagulation assists in timely and specific diagnosis of existing coagulopathy. Standard monitoring including PTT, aPTT, PTL count, fibrinogen and international normalized ratio (INR), gives information on the state of initial coagulation and 4% of thrombin production[50] and often provides false negative results. Complete and rapid monitoring of coagulation and fibrinolysis with viscoelastic tests is more accurate for targeting the treatment and avoiding FFP and PRCBs. Algorithms by ROTEM/TEG provide optimal approach for haemostatic treatment, but these viscoelastic tests have certain limitations; defects in primary haemostasis cannot be diagnosed, they cannot predict bleeding during or after surgery, TEG cannot distinguish between coagulopathy by dilution and thrombocytopenia and finally, there is a lack of sensitivity to platelet dysfunction which is due to antiplatelet drugs.[51] Very often ROTEM/TEG is not available, and in order to start with early coagulation support, protocol for massive bleeding patients

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will depend on rationale strategy which relies on the resources available. This strategy for preventing and stopping the development of critical bleeding was presented by Grotke O and Rossaint R[52] at the International Symposium of Intensive Care Medicine (ISICM) 2015 in Brussels, and it includes three phases. In the first one, the goal is to stop fibrinolysis, in the second, to allow thrombin formation,[53] and finally, in the third stage, to increase thrombin formation. If the stages are accepted, this strategy should lead to successful haemostasis. In terms of the first stage, hyper fibrinolysis should be considered early and TXA is recommended immediately. Tranexemic acid should be given in massive bleeding, even in the absence of clinically diagnosed hyper fibrinolysis and the optimal dose is 10-20 mg/kg/tt.[54] When hyperfibrinolysis is considered, then in the second step, fibrinogen and PTL have to be administered in order to provide thrombin formation. During the massive bleeding fibrinogen reaches critically low levels before the platelets and other coagulation factors.[55] Fibrinogen level is decreased in injured patients on admission and is associated with poor outcomes and serves as an independent predictor of mortality at 24 h and 28 days.[56] By using ROTEM rapid assessing of hypo fibrinogenemia might be performed. A dose of 4-8 g of purified human fibrin concentrates are recommended, but fibrinogen can be compensated also through administration of other fibrin supplements such as cryoprecipitate and FFP. Fresh frosen plasma contains relatively little fibrinogen (~ 500mg/250 ml), but it is not known exactly how much.[55] If bleeding is acute in the absence of ROTEM/TEG, fibrin concentration can be measured in plasma. Standard laboratory tests, such as hematocrit and base excess correlate with plasma fibrin values. Along with fibrinogen for effective thrombin formation the crucial role plays administration of platelets. Fibrinogen supplementation could partially compensate thrombocytopenia, but severe thrombocytopenia can disrupt the creation of thrombus even if the values of fibrinogen and thrombin formation are normal. Platelets are administrated only if the patient is bleeding continuously (the goal is to achieve target of 50 x 109/L) and if there is clear deficiency of PTL. For successful haemostasis the last stage is important, that is, the increase of thrombin formation. Bleeding that continues despite fibrin supplementation and adequate number of PTL may be as a result of insufficient thrombin formation which is a predictor of mortality in trauma-induced coagulopathy. In those cases, PCCs may be the first line therapy for thrombin deficiency in major bleeding, but there are not enough reports on the use of PCCs in massive bleeding. However, if viscoelastic tests are not available, INR may be considered to prevent potentially non-adequate PCCs therapy or to avoid delay in treatment due to longer time in getting other standard laboratory tests. But, INR has a limited value for PCCs therapy in emergency situations and it is unreal surrogate marker for bleeding. The lowest possible dose of PCCs is recommended to be ≤ 20 IU/kg/tt.[57] If there is no PCCs, rFVIIa is an option. Recombinant-activated factor VII is taken into account when first-line treatment (combination of surgical control, angiographic embolization and control use of blood products), fails to control bleeding. In the absence of monitoring of the overall haemostasis, administration of rFVIIa and PCCs is unacceptable. The mechanism of action of rFVIIa suggests enhancement of haemostasis, which is limited to the site of injury without the activation of the coagulation process.[47] Therefore, its use in traumatic haemorrhage is rational. Despite "off-label" use of rFVIIa, it can be used in conditions of uncontrolled haemorrhage.[44,58] Use of rFVIIa should be by consensus between surgeon, intensivist and haematologist when the patient is at risk to die from uncontrolled bleeding due to coagulopathy. For the expanding off-label clinical uses of rFVIIa, more randomized controlled trials are nedeed.

Regarding these three phases, it is assumed that in trauma-induced coagulopathy hyperfibrinolysis is an important carrier of trauma-induced coagulopathy; fibrinogen is the first factor that goes "down" and thrombin generation is not the initial problem. Thus, TXA can improve the stability of the clot, fibrinogen can improve the quality of clot, PCCs can improve thrombin creation, and FXIII can improve the stability/quality of clot.

Conclusion

In conclusion, massive haemorrhage in trauma patients has to be controlled on time; otherwise it will result in death. The treatment strategies should focus on achieving surgical haemostasis as soon as possible and correcting coagulopathy. The current recommendations are helpful, but cannot be applied in every situation. The availability of resources is crucial.

Conflicts of interest

We, authors, declare that there is no any financial interest and any conflict of interest associated with this publication.

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