Review Article

Treatment of Acute Coagulopathy Associated with Trauma

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Coagulopathy is frequently present in trauma. It is indicative of the severity of trauma and contributes to increased morbidity and mortality. Uncontrolled bleeding is the most frequent preventable cause of death in trauma patients reaching hospital alive. Coagulopathy in trauma has been long thought to develop as a result of hemodilution, acidosis, and hypothermia often related to resuscitation practices. However, altered coagulation tests are already present in 25–30% of severe trauma patients upon hospital arrival before resuscitation efforts. Acute coagulopathy associated with trauma (ACoT) has been recognized in recent years as a distinct entity associated with increased mortality, morbidity, and transfusion requirements. Transfusion and nontransfusion strategies aimed at correcting ACoT, particularly in patients with massive bleeding and massive transfusion, are currently available. Early administration of tranexamic acid to bleeding trauma patients safely reduces the risk of death. It has been proposed that early aggressive blood product transfusional management of ACoT with a red blood cell : plasma : platelets ratio close to 1 : 1 : 1 could result in decreased mortality from uncontrolled bleeding.

1. Introduction

Trauma is the main cause of death in people under 40 years and contributes to 10% of deaths worldwide. Up to 40% of trauma deaths are secondary to uncontrolled bleeding, constituting the leading cause of trauma hospital mortality (within the first 48 hours of evolution) and therefore a preventable cause of death [1].

It is recognized that coagulopathy can be present in the early stages of trauma, with altered coagulation tests being found in up to 30% of cases at the time of hospital admission [2]. Thus, acute coagulopathy associated with trauma (ACoT) seems to be a manifestation of the severity of the injuries sustained and the degree of shock. It is associated with higher mortality and greater transfusion requirements [3, 4]. Currently, both transfusion and nontransfusion strategies exist, which are aimed at correcting ACoT, particularly in patients with massive bleeding and massive transfusion (MT) and may result in a decrease in mortality from uncontrolled bleeding.

This paper will review ACoT, with particular emphasis on its treatment.

2. Acute Coagulopathy Associated with Trauma

Coagulopathy is a common phenomenon in traumatized patients as well as a marker of injury severity. Abnormal coagulation favors continuous loss of blood, increasing the risk of morbidity and death from uncontrolled bleeding. Coagulopathy in trauma has long been considered to develop after the initial injury due to acidosis, hypothermia, loss and hemodilution of coagulation factors as a consequence of shock, and agressive intravenous fluid resuscitation [5]. More recently, it has been recognised that 25% to 30% of patients show alterations in coagulation tests upon hospital arrival [2, 6], before receiving large amounts of fluids and prior to the appearance of hypothermia and acidosis. Accordingly, it has been proposed that, in early stages, coagulopathy directly associated with trauma and shock can develop. This condition has been termed "acute coagulopathy of trauma" (ACoT) and is an indicator of poor prognosis independent of injury severity. ACoT is associated with increased mortality (up to 8 times and 4 times increase at 24 hours and 30 days resp.),

more blood transfusions, longer ICU and hospital stay, and higher incidence of multiple organ failure [5, 7].

The precise physiopathology of ACoT is still unclear, but likely multifactorial and related to the severity of trauma and degree of shock, given the higher incidence with increasing injury severity score (ISS). Two main mechanisms have been proposed. The first is the activation of protein C (APC) secondary to hypoperfusion due to massive bleeding. APC inactivates factors VIII and V and increases fibrinolysis due to consumption of antifibrinolytics (plasminogen activator inhibitor and thrombin activatable fibrinolysis inhibitor) [8, 9]. Increased fibrinolysis is enhanced by the release of tissue plasminogen activator (tPA) secondary to tissue damage. The second mechanism poses that endothelial damage and tissue factor exposure generate disseminated intravascular coagulation (DIC) with subsequent increase in thrombin generation, microthrombosis, and consumption of coagulation factors [8]. The latter mechanism has been challenged by authors who consider hypoperfusion to be the key element in the development of ACoT, to the point that they have entitled it as (Acute Coagulopathy of Trauma-Shock) ACoTS [10]. Several studies have found that ACoT is practically absent in patients with a base deficit less than 6 mmol/L, independently of ISS value, illustrating the importance of hypoperfusion [11, 12]. In addition, the absence of microvascular thrombosis that is characteristic of DIC has been reported [13]. Regardless of the initial mechanisms of ACoT, coagulopathy will continue to worsen if hemodilution, acidosis, and hypothermia develop due to an inadequate treatment [5].

3. Diagnosis of Acute Coagulopathy Associated with Trauma

The presence of ACoT should be considered in all trauma patients, especially when high-energy trauma is involved. A high degree of suspicion must be maintained when there is evidence of significant bleeding (tachycardia, weak pulses, hypotension, impaired consciousness, oliguria, signs of poor clinical perfusion, etc.), hypoperfusion (base deficit greater than 6 mmol/L and an increase in lactate), and particularly in patients with severe injuries [7]. Unfortunately, the lack of well-defined diagnostic criteria for ACoT impedes early identification and treatment. Prolongation of prothrombin time (PT) and activated thromboplastin time (APTT) have been used by most authors to diagnose ACoT [5]. Brohi et al. established the presence of ACoT if PT and APTT were 1.5 times over the normal values [6]. While these tests are simple and widely available, they have several limitations. PT and APTT reflect hemostasis in plasma (as opposed to whole blood), during the first 60 seconds of clotting (whereas the complete coagulation process lasts between 15 to 30 minutes), and exclude the fibrinolysis stage from the analysis. Additionally, these tests have a turnaround time of 30–45 minutes, are carried out at 37°C and pH 7.5, and do not consider the presence of hypothermia, acidosis, hypocalcemia, or anemia [8]. The use of devices that allow for rapid determination of PT and APTT (point of care) has been proposed. Although the use of these devices allows rapid availability of results, they still have to be validated.

The use of thromboelastography (TEG) and rotation thromboelastometry (ROTEM) to diagnose ACoT has been proposed, since both techniques allow complete evaluation of coagulation (beginning, speed, and extent of the clot formation) and fibrinolysis. A positive correlation between TEG, ROTEM, and traditional coagulation tests (PT, APTT, INR) has been reported. These tests enable the evaluation of trauma-associated hyperfibrinolysis and, thus, could be useful in the prediction of transfusion requirements [14, 15]. Some limitations of TEG and ROTEM are the limited availability of the equipment, need for operator training, prolonged results turnaround time (30 minutes), and lack of established cut-off points for the diagnosis of ACoT.

4. Damage Control Resuscitation

Damage control resuscitation (DCR) is a treatment approach that targets the conditions that exacerbate hemorrhage after trauma, carrying out a hemostatic resuscitation strategy to avoid death from uncontrolled bleeding. DCR involves early control of bleeding through interventional and surgical procedures (damage control surgery) and administration of blood products and coagulation factors to ensure adequate oxygen transport and correction of coagulopathy [16]. For this purpose, the administration of all blood products, permissive hypotension, controlled administration of crystalloids to avoid hemodilution, and the early correction of hypothermia, acidosis, and hypocalcemia are needed. Damage control surgery focuses on promptly controlling bleeding and contamination (hollow viscus injuries), limiting exposition time to avoid progression of acidosis and hypothermia, and deferring definitive reconstructions once the patient has been stabilized and homeostasis restored [4].

The transfusion support emphasizes early administration of all blood products and not only red blood cells (RBC), with particular attention to plasma. In recent years, the transfusion of all components of blood products with a 1 : 1 : 1 ratio of plasma to RBC to platelets has been proposed in cases of massive bleeding and MT. This strategy aims at early correction of ACoT.

5. Massive Transfusion

Massive transfusion (MT) means massive bleeding and is defined by the loss of more than one entire blood volume (equals to 70 mL/kg of weight) within 24 hours [4]. Massive bleeding translates in greater morbidity and mortality. ACoT is associated with massive bleeding and risk of MT [17]. Therefore, early correction could improve the prognosis of affected patients. MT is traditionally defined as the transfusion of 10 or more units of RBC within 24 hours. Other definition of MT is the need to transfuse 4 or more units of RBC in one hour or the replacement of more than 50% of the entire blood volume within 3 hours [4].

The concept of MT has been subject to criticism by several authors, arguing that it is an arbitrary definition [18].

Stanworth et al. [19], upon reviewing almost 6000 trauma patient registries from 5 databases, found that mortality increased with greater number of RBC transfused but was unable to find a cut-off point. Despite of the possible limitations of this concept, it is an operational definition and at the moment no method to exactly estimate blood loss exists, which explains its wide use.

Trauma is the most frequent cause of MT, with greater occurrence in war-related trauma. MT is present in only 2-3% of civilian trauma cases. Regardless of the type of trauma, MT is linked to increased mortality rates, as high as 80% [3]. Additionally, patients that require MT can consume up to 70% of the transfusions in trauma [20].

6. Prediction of Massive Transfusion

One of the challenges in treating patients with massive bleeding and MT risk is the early prediction of these factors. Waiting until the patient complies with the classic criteria for MT (transfusion of 10 or more units of RBC within 24 hours) is insufficient, considering that patients can develop coagulopathy very early in their evolution.

It is safer to consider that patients at risk of developing ACoT (see above), as well as those that do not respond or respond partially to fluid administration (transient normalization of hemodynamics parameters), are at higher risk of suffering from massive bleeding [1].

Several models that attempt to predict the need for MT have been developed, such as McLaughlin, TASH, ABC, and PWH scores. These scores include hemodynamic variables, laboratory exams, and the presence of specific injuries. All these models have a good capacity to predict the need for MT [21, 22]. However, their use has not proliferated, probably because they include variables that are not always available upon patient's admission. Several authors have proposed that ACoT should be considered a key risk factor for massive bleeding. Therefore, a prompt definition of ACoT diagnostic criteria is fundamental.

TEG and ROTEM have been evaluated as MT predictors, with good results reported in the "clot firmness" parameter, which can be rapidly determined [23, 24].

7. Treatment of Acute Coagulopathy Associated with Trauma

7.1. Blood Products. Several studies have reported that patients requiring MT who received blood products with a 1 : 1 : 1 ratio had lower mortality rates and required fewer total transfusions [25–38]. The body of evidence that supports this strategy is mainly retrospective and originally reported in war-related trauma cases (Table 1).

Borgman et al. [25] in 2007 reported that in patients with combat-related trauma who required MT, a high plasma to RBC ratio (1 : 1.4) was associated with improved survival, in comparison to patients that received an intermediate (1 : 2.5) or low ratio (1 : 8). These findings have been confirmed in civilian trauma and some authors have expanded these results to other blood products. Duchesne et al. [26] reported

a lower mortality rate (26% versus 87.5%) in patients with MT that received a high (1 : 1) versus a low (1 : 4) ratio of fresh frozen plasma (FFP) to RBC. Maegele et al. [27] in a multicenter German study, also found that an FFP to RBC ratio close to 1 : 1 was associated with a decrease in mortality rates. In a recently published meta-analysis, Bhangu et al. [28] reported that a plasma to RBC ratio higher than 1 : 2 resulted in a significant reduction in mortality compared to lower ratios; however, ratios of 1 : 1 were not proven to confer additional benefit beyond ratios of 1 : 2. Holcomb et al. [29], in a retrospective study in 16 level 1 trauma centers in U.S.A., found that the combination of high plasma and high platelets to RBC ratios were associated with increased survival. Stinger et al. [30] reported that the transfusion of cryoprecipitates to achieve a ratio of 0.2 grams of fibrinogen/RBC unit was associated with improved survival. These results are particularly interesting, taking into account that increased fibrinolysis is considered a main component of ACoT. Some authors have studied the usefulness of MT protocols along with evaluating the effect of the ratio between blood products. Dente et al. [31] compared the effect of an MT protocol with a high FFP and platelets to RBC ratios against historic controls, reporting an improvement in blunt trauma survival.

Not all studies that have evaluated a high ratio between different blood products have found positive results [39–42]. Kashuk et al. [40] found a U-shaped distribution for predicted mortality, with the lowest mortality between an FFP to RBC ratio of 1 : 2 to 1 : 3. Mitra et al. [41] found that, although a low FFP : RBC ratio was an independent risk factor of mortality, the effect was lost when excluding patients that died within the first 24 hours. This study shed light on a point that has been a source of controversy. FFP, unlike RBC that can be used immediately, must be thawed prior to administration. Therefore, early death could explain the low FFP : RBC ratio, and not vice versa. On the other hand, several of the studies that have reported a decrease in mortality rates have also found an increase in complications associated to transfusions [25, 27, 37, 38, 41].

Many of these studies have concluded that the improvement in survival could be attributed to a decrease in deaths due to uncontrolled bleeding [25, 29–31, 36], reflected in less total transfusions [34, 38]. However, there is no consensus regarding this proactive transfusion strategy. For example, the European guidelines for "Management of Bleeding Following Major Trauma" [43] recommend administering plasma at an early stage, at a dose of 10 to 15 mL/kg, without endorsing a specific plasma to RBC ratio. Considering that up to date there are no randomized controlled trials (RCT) that have evaluated the ratios between blood products in trauma patients requiring MT, it seems appropriate to administrate RBC, FFP, platelets, and cryoprecipitates early upon hospital arrival to patients with severe injuries and risk of massive bleeding. At this time it is not possible to recommend a specific ratio.

Finally, it is important to emphasize that this proactive transfusion strategy is not recommended for patients with minor trauma and for those that have already been stabilized. A restrictive RBC transfusion strategy in stable trauma patients has been proven to be feasible and not

TABLE 1: Studies evaluating a high relation between blood products in trauma patients with massive transfusion.

Author	Study characteristics	Main results	Complications
Borgman et al. [25]	Retrospective, 1 field hospital, 246 patients	A plasma to RBC ratio closet to 1:1 was associated with improved survival	Increase in MOF and sepsis with a high plasma to RBC ratio
Duchesne et al. [26]	Retrospective, 1 level I trauma center in USA, 135 patients	An FFP to RBC ratio close to 1:1 was associated with improved survival	Not reported
Maegele et al. [27]	Retrospective, multicenter German study, 713 patients	An FFP to RBC ratio close to 1:1 was associated with a decrease in mortality rates	Septic complications and MOF increase in the FFP to RBC high ratio group
Holcomb et al. [29]	Retrospective, 16 level I trauma centers in USA, 466 patients	The combination of high FFP and high platelets to RBC ratios was associated with increased survival	The combination of high FFP and high platelets to RBC ratios was associated with increased ICU, ventilator and hospital-free days
Stinger et al. [30]	Retrospective, 1 field hospital, 252 patients	The transfusion of an increased fibrinogen to RBC ratio was associated with improved survival	Not reported
Dente et al. [31]	Prospective, 1 level I trauma center in USA, MT protocol (116 patients) versus historical controls	Increased FFP to RBC and platelets to RBC ratios according to an MT protocol were associated with improved survival in blunt trauma	Not reported
Gunter et al. [32]	Retrospective, 1 level I trauma center in USA, 158 patients (MT protocol)	Increased FFP to RBC and platelets to RBC ratios according to an MT protocol were associated with improved survival	Not reported
Perkins et al. [33]	Retrospective, 1 field hospital, 694 patients	High platelets (apheresis) to RBC ratios were associated with increased survival	No difference between groups
Zink et al. [34]	Retrospective, 16 level I trauma centers in USA, 466 patients	The administration of high ratios of FFP to RBC and platelets to RBC improves survival and decreases overall RBC transfusions	The administration of high platelets to RBC ratios was associated with increased ventilator-free days
Shaz et al. [35]	Prospective, 1 level I trauma center in USA, MT protocol versus historical controls, 214 patients	The administration of high ratios of plasma, platelets, and cryoprecipitates to RBC increased survival	Not reported
Johansson et al. [36]	Before and after study using historical controls, university hospital in Denmark 832 patients, (MT protocol guided by TEG)	An MT protocol guided by TEG ensuring high FFP and high platelets to RBC ratios was associated with improved survival	Not reported
Holcomb et al. [37]	Retrospective, 22 level I trauma centers level 1 in USA, 643 patients	Transfusion of platelet:RBC ratios of 1:1 was associated with improved survival	Transfusion of platelet:RBC ratios of 1:1 was associated with increased FOM
Sperry et al. [38]	Multicenter, prospective USA cohort study, 415 patients (blunt trauma)	An FFP to RBC ratio >1:1.5 was associated with a significant lower risk of mortality	A FFP:RBC ratio >1:1.5 was associated with a higher risk of ARDS
Snyder et al. [39]	Retrospective, 1 level 1 I trauma center in USA, 134 patients	An FFP to RBC ratio close to 1:1 was associated with improved survival. However, after adjustment for survival bias, the association was no longer statistically significant	Not reported
Kashuk et al. [40]	Retrospective, 1 level I trauma center in USA, 133 patients	The adjusted mortality OR FFP to RBC ratio follows a U-shaped association	Not reported
Mitra et al. [41]	Retrospective, 1 level I trauma center in Australia, 331 patients	After excluding deaths in the first 24 hours, the FFP:RBC ratio had no association with mortality	The administration of a high FFP to RBC ratio was associated with increased ventilator and ICU days
Teixeira et al. [42]	Retrospective, 1 level 1 I trauma center in USA, 383 patients	The mortality rate decreased with increased FFP transfusion. However, it does not seem to be a survival advantage after a 1:3 FFP:PRBC ratio has been reached	Not reported

associated with increased mortality or morbidity [44]. Furthermore, transfusions have well-known risks (acute lung injury, transfusion-related lung injury, multiple organ failure, increase risks of infections, etc.) and considerable costs, reaching up to 30% of the total ICU costs in trauma patients [45].

7.2. Pharmacological Treatment. In addition to the transfusional management of ACoT, the administration of antifibrinolytics and coagulation factors have also been investigated. The most studied antifibrinolytic has been tranexamic acid (TXA). TXA inhibits plasminogen activation, as well as plasmin activity, preventing fibrin clot lysis. The CRASH-2 study [46] evaluated the use of TXA versus placebo in trauma within 8 hours of injury. This was a multicenter RCT that recruited more than 20,000 trauma patients with hemodynamic compromise or at risk of significant bleeding. The study showed that the use of TXA was associated with a decrease in mortality and deaths resulting from bleeding, without an increase in thrombotic complications. Paradoxically, transfusions did not decrease with the use of TXA. Based on the key role of hyperfibrinolysis in ACoT pathogenesis and the results of CRASH-2, several authors have proposed that the use of TXA should be a standard in trauma management [47].

Two RCTs have evaluated the use of activated factor VII (rFVIIa) in trauma. This agent, originally developed for the treatment of hemophilia A or B, acts enhancing the thrombin production. Boffard et al. [48] could not demonstrate a difference in mortality or morbidity comparing rFVIIa to placebo, despite finding a decrease in RBC transfusions in blunt trauma patients. Recently, the control study [49], which also compared rFVIIa to placebo, was terminated early due to futility. This trial also found a decrease in transfusion requirement but no mortality difference. Given these results and its elevated cost, rFVIIa is currently recommended only as a final option in controlling massive bleeding in blunt trauma (after surgery, interventional procedures, and blood transfusion) [43].

Prothrombin complex concentrate (PCC) and fibrinogen concentrate have been proposed as an alternative to the plasma and cryoprecipitates. PCC contains vitamin K-dependent factors (factors II, VII, IX, and X) and natural anticoagulants (proteins C, S, and Z). Possible advantages in using these factor concentrates are avoiding fluid overload, obtaining adequate levels of coagulation factors faster than those with plasma, and decreasing transfusion-associated complications [7, 50]. Given that hyperfibrinolysis appears to be a key element in the pathogenesis of ACoT, fibrinogen concentrate could have an important role in its treatment. In such cases, it has been proposed that TXA should be administered first [13]. Schöchl et al. [51] retrospectively compared the use of PCC plus fibrinogen concentrate versus FFP in patients with severe trauma and altered coagulation tests compatible with ACoT. The group treated with coagulation factors received less RBC and platelet transfusions and had less MT requirements and a lower incidence of MOF. While these results are interesting, at this time, recommendations for the use of these concentrate factors in trauma are limited. PCC is actually indicated for emergency reversal of vitamin K-dependent oral anticoagulants [7]. Fibrinogen concentrate is recommended as an alternative to cryoprecipitates in bleeding patients with plasma fibrinogen levels less than 1.5–2 g/L [43].

8. Conclusions

Uncontrolled bleeding is the most frequent preventable cause of death in trauma patients. Early correction of acute coagulopathy associated with trauma through damage control resuscitation is a promising strategy to decrease preventable trauma death.

Early use of all blood products with a ratio close to 1 : 1 : 1 seems to improve survival of patients with massive bleeding. However, these findings must be corroborated prospectively in randomized control trials. A restrictive transfusion strategy is safe and appropriate in stable patients.

Early administration of tranexamic acid is recommended for all trauma patients with a significant risk of bleeding as it reduces the risk of death.

Conflict of Interests

The authors declare that they have no conflict of interests.

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