Transfusion and trauma – Future strategies

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Manuscript Number: ACO2202c

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Kommentar [OMT1]: Muss <200 sein, AKTUELL OK mit 199 Words

Kommentar [d2]: Mit diesen Modifikationen hat es nun 198 Wörter.

Abstract

Purpose of review: Major trauma is often associated with hemorrhage and transfusion of blood and blood products, all associated with adverse clinical outcome. The aim of this review is to emphasize why bleeding and coagulation has to be monitored closely in trauma patients and to discuss the rationale behind modern and future transfusion strategies.

Recent findings: Hemorrhage is a major cause of early death after trauma. Besides the initial injuries, hemorrhage is significantly promoted by coagulopathy. Early identification of the underlying cause of hemorrhage with coagulation tests (routine and bedside) in conjunction with blood gas analysis allow early goal-directed treatment of coagulation disorders and anemia thereby stopping bleeding and reducing transfusion requirements. These treatment options have to be adapted to the civilian and non civilian sector. Transfusion of blood and its components is critical in the management of trauma hemorrhage, but is per se associated with adverse outcome. Decisions must weigh the potential benefits and harms.

Summary: Future transfusion strategies are based on early and continuous assessment of the bleeding and coagulation status of trauma patients. This allows specific and goal-directed treatment, thereby optimizing patient's coagulation status early, minimizing exposure to blood products, reducing costs and improving patient's outcome.

Keywords: Blood management, transfusion, hemorrhage

Introduction

Kommentar [OMT3]: 50-100

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Hemorrhage is known to be a major cause of early death after injury and has been shown to be responsible for 30% to 40% of trauma mortalities [1-3]. Furthermore, hemorrhage with consecutive multiple transfusions has been shown to significantly worsen clinical outcomes.[4,5]

Management priorities in trauma patients are to ensure adequate ventilation, oxygen delivery, hemorrhage control and to restore tissue perfusion to vital organs. Early and continuous re-assessment of the bleeding and coagulation status of trauma patients allows specific goal-directed treatment, thereby optimizing patient's coagulation status, minimizing exposure to blood products, reducing costs and improving patient's outcome.[6,7]

Mechanism of hemorrhage in trauma patients

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Gilt fuer gesamtes review exkl Refs

Kommentar [d5]: Den NEUEN Mechanismus (im Abstract angekündigt) sollte hier exakt beschrieben warden mit 1-2 Figuren um zu erklären warum es zu einer Hypokoagulation kommt und gleichzeitig zu einer Hyperfibrinolyse – Das ist einer der WICHTIGSTEN Kommentare

Hemorrhage reduces preload required to ensure adequate cardiac output and peripheral oxygen delivery. Inadequate tissue perfusion, not always associated with overt hypotension, can trigger a neuro-humoral cascade, leading to sequential organ failure. Mortality from established organ failure has not changed since it was first described almost 30 years ago [8]. Diagnosing and treating hemorrhage early remains imperative. The American College of Surgeons has developed the classification scheme stratifying blood loss from Stage 1 (<15% of total circulating blood volume) to Stage 4 (>40% of total circulating blood volume) [9]. Young people in good health may compensate well for large-volume blood loss, up to 50% of the total circulating blood volume. Then, they may

develop sudden cardiovascular compromise when compensatory mechanisms fail. Elderly people on the other side may tolerate much smaller blood losses only.

Anatomical bleeding

Active hemorrhage as a result of major injuries is life-threatening and leads to hemorrhagic shock and exsanguination if not treated readily. Bleeding may be stopped temporarily by external compression and tourniquets, however, surgical or interventional (e.g., arterial embolization) repair is required for final hemorrhage control.

Coagulopathic bleeding

An abnormal coagulation status is frequently present early after major trauma at admission to the emergency department and is associated with a 5-fold increase in mortality [10-13]. Traditionally, the acute traumatic coagulopathy has been thought to be due to consumption of coagulation factors, dilution from intravenous fluid therapy, hypothermia, and metabolic acidosis. However, it has recently been shown that none of these factors is initially responsible for the acute traumatic coagulopathy. These factors become significant only in the later phase of traumatic coagulopathy. Studies by Brohi et al [11-14] have described an early and previously unknown acute traumatic coagulopathy before any of the above mentioned traditional causes (lethal triade) of acute traumatic coagulopathy were present. These studies have shown that coagulopathy and mortality as well as transfusion requirements are to by linked with hypoperfusion of tissues and the protein c-pathway, this was also proven for traumatic brain injury. Low protein C levels are associated with prolongation of the partial thromboplastin and prothrombin times and hyperfibrinolysis with low levels of plasminogen activator inhibitor-1 and high D-dimer

levels. High thrombomodulin and low protein C levels are associated with increased mortality, blood transfusion requirements, acute renal injury, and reduced ventilator-free days.

The pathophysiology of fibrinolysis in association with injury is exacerbated by shock and this is mediated by deinhibition of tissue plasminogen activator through the consumption of plasminogen activator inhibitor-1. A low level plasminogen activator inhibitor-1, in combination with an increased release of plasminogen activators from the vessel wall will result in hyperfibrinolysis. Actually it seems that thrombin activatable fibrinolysis inhibitor is the main driver of fibrinolysis inhibition, and that reduction in thrombin activatable fibrinolysis inhibitor activation by the competitive binding of protein C to thrombin–thrombomodulin is the mechanism for derepression of fibrinolysis with activation of protein C. The consumption of plasminogen activator inhibitor-1 by activated protein C seems to be the most important clinical cause of hyperfibrinolysis.

Diagnosis and monitoring of bleeding

Assessment of hemorrhage and volume status. Blood pressure and heart rate are vital signs which are nonspecific to evaluate hemorrhage. Mixed and central venous oxygen saturation are more sensitive and reliable measurements of acute volume loss [15-17]. The degree of metabolic acidosis, as measured by the base deficit from an arterial blood gas sample, is helpful to evaluate the degree of shock. Base deficit has been shown to correlate with transfusion requirements, ICU stay, and ultimate outcome [18,19]. During initial resuscitation, base deficit typically correlates with serum lactate level. Interestingly, the ability to clear lactate to normal is one of the most important predictors

of survival following hemorrhage and injury [20-22]. Serial blood gas determinations (arterial and venous) may be helpful in determining whether blood loss is continuing or not.

Assessment of coagulation. Most commonly, routine laboratory-based coagulation tests (e.g., PT/INR, aPTT, fibrinogen), platelet numbers and hemoglobin concentration (Hb) are being used to assess the patients' current coagulation status [23]. However, the value of these tests has been questioned in the acute bleeding situation because there are delays from blood sampling to obtaining results (45–60 min), coagulation tests are determined in plasma rather than whole blood, no information is available on platelet function and the assays are performed at a standard temperature of 37°C rather than the patient's temperature [24].

Point-of-care coagulation monitoring devices assessing the viscoelastic properties of the developing clot in whole blood, e.g., thrombelastography (TEG®) or rotation thrombelastometry (ROTEM®), may overcome several limitations of routine coagulation tests [25,26]. In particular, these technologies allow to assess in vivo coagulation system interactions with platelets and red blood cells and provide useful information on platelet function [27]. In addition, they may be performed at the bedside allowing faster turnaround times. Furthermore, the clot development can be visually displayed in real-time, the assay is fibrinolysis sensitive, and the coagulation analysis can be done at the patient's temperature [28]. Nevertheless, results obtained from these in vitro tests must be carefully interpreted in the clinical context.

Present and future transfusion practice in trauma patients

Prevention of further bleeding

The initial phase after trauma - from injury to surgery/intervention – has to be minimized and further bleeding should be prevented. Hill et al [29] observed a significant decrease in mortality from shock by establishing a 60 minute emergency department time limit for patients in hemorrhagic shock. Additionally, Hoyt et al [30] showed that delayed transfer to theatre is an avoidable cause of death which can be minimized by reducing the time for diagnosis and resuscitation prior to surgery.

Without brain injury, a target systolic blood pressure of 80 to 100 mm Hg should be maintained until the major bleeding is stopped.[6] Aggressive fluid therapy to preserve tissue oxygenation and to restore the circulating blood volume leads to dilution of coagulation factors, hypothermia, increased hydrostatic pressure and further bleeding. The concept of low-volume fluid resuscitation, called 'permissive hypotension', prior to surgical source contol maintains tissue perfusion at a lower level but sufficient for a short period of time without the adverse effects mentioned above [31]. The low-volume approach is not to be applied in traumatic brain and spinal injuries as an adequate perfusion pressure is crucial to ensure tissue oxygenation of the injured central nervous system.

Transfusion of red blood cells (RBC)

Hemoglobin based transfusion triggers. According to current guidelines from the American Society of Anesthesiologist, RBC transfusion is recommended if the hemoglobin concentration drops below 6-10g/dl. Transfusions over 10 g/dl are rarely

indicated and, transfusions seem almost always indicated if hemoglobin falls below 6 g/dl. [32] In Europe, a Hb target range of 7-9 g/dL is largely accepted in major trauma.[6]

Physiological transfusion triggers on the other hand are tachycardia, hypotension, oxygen extraction greater than 50%, mixed venous oxygen pressure of less than 32 mm Hg, increase of lactate and ECG changes [6,33,34]. The depth of shock, hemodynamic response to resuscitation, and the rate of actual blood loss in the acutely bleeding and hemodynamically unstable patient may also be integrated into the indication for RBC transfusion[35]. However, RBC transfusions should be used restrictively [36].

Alternatives to allogeneic red cell transfusion

In trauma, the only available alternative to allogeneic RBC transfusion in clinical practice is currently the intraoperative cell salvage. It has been shown efficacious for reducing allogeneic blood transfusions [37]. The quality of salvaged blood seems to be better compared with stored packed RBCs, with less risk for the patient [37]. However, cell salvage is only applicable when the operative site not contaminated.

Artificial oxygen carriers may represent a future alternative to RBC transfusions. There are two groups of artificial oxygen carrier currently under development: Synthetically manufactured perfluorocarbons, and hemoglobin-based oxygen carriers [38]. However,none of these products has achieved market approval for Europe, US or Canada so far.

Transfusion of fresh frozen plasma (FFP) and platelets

Traditional indications for fresh frozen plasma are massive bleeding due to multiple factor deficiencies, emergency reversal of vitamin K antagonists, and treatment of

thrombotic thrombocytopenic purpura (TTP) [32]. However, the clinical efficacy of FFP is largely unproven[6,39]. Large quantities of FFP (15 ml/kg body weight and more) are recommended to achieve an effect in massive bleeding [6,40,41,]. Interestingly, there are only expert-opinion but no evidence based transfusion thresholds published for FFP administration [32,42]. However, there are significant adverse effects associated with FFP transfusions including volume overload (TACO), allergic reactions, transfusion-related acute lung injury (TRALI), transmission of infectious pathogens [40,43,44] and a 3 fold increase of nosocomial infections [45].

In a bleeding patient, platelets should be kept >50 x 10^3 /µl, and >100 10^3 /µl in patients with traumatic brain injury [6,7]. Adverse effects of platelets are similar to FFP, except the much higher risk of bacterial contamination [46]. Therefore, the indication to transfuse platelets is to be restrictive. As for FFP, there are only expert-opinions available for the indication of platelet transfusion, no studies on an evidence based level are available so far.

Replacement of specific coagulation factors

Fibrinogen. Fibrinogen is the substrate to form a clot. Several in-vitro and animal studies have shown that fibrinogen substitution is essential to reverse dilutional coagulopathy [47-49]. Furthermore, several human studies (civilian and non-civilian) confirmed these data, showing that early and aggressive replacement of fibrinogen in patients with severe hemorrhage and dilutional coagulopathy improves clot strength significantly and may lead to better survival [50-53].

Factor XIII. Factor XIII is the key coagulation factor to stabilize the clot. Schroeder et al and Nielsen et al [54-56] have proven a relation between decreased factor XIII activity and reduced clot firmness (MCF) by computerized thrombelastography. Trauma and major hemorrhage is known to be a cause of acquired factor XIII deficiency [57]. It seems reasonable to substitute factor XIII early, thereby improving clot firmness and reducing bleeding [58] as well as the use of blood products [59,60].

Prothrombin complex concentrate. Prothrombin complex concentrates (PCC) provide a source of the four vitamin K dependent coagulation factors, and consequently, PCC is recommended both in Europe and the USA for emergent reversal of oral anticoagulants [61-65]. Furthermore, Bruce and Nokes [66] recently demonstrated that the use of PCC in trauma patients leads to a considerable reduction in the use of blood products (FFPs, RBCs and cryoprecipitate) and that survival improved and bleeding stopped earlier. Therefore, PCC might have a place in control of trauma related bleeding, although this indication is currently off label.

rFVIIa. Recombinant activated factor VIII (rFVIIa) leads to a "thrombin burst" thereby transforming fibrinogen into fibrin. Before treating patients with rFVIIa, patients should fulfill certain criteria, for example thrombocytopenia and hypofibrinogenemia must be corrected [67-69]. One study in trauma has shown a reduction in RBC transfusions in rFVIIa treated patients [70]. However, rFVIIa is not an alternative to surgical bleeding control, and its use in trauma is still an off label indication. Risks and benefits have to be carefully evaluated before usage and economic aspects taken into consideration [71].

Pharmacologic agents

Antifibrinolytics, such as aminocaproic acid (ε-aminocaproic acid) and tranexamic acid are used to inhibit overt fibrinolysis, which act by blocking the lysine-binding site on plasmin. [6]

Protamine sulfate reverses the anticoagulant effects of heparin by binding to it. It is a highly cationic peptide. It binds to heparin to form a stable ion pair which does not have anticoagulant activity.

Specific goal-directed transfusion, transfusion algorithms

Algorithms display decision-making treatment processes and problem-solving strategies by giving clearly defined and formalized guidelines. With the help of clinical algorithms, highly complex processes such as the management of the bleeding can be translated into a clearly structured, logical pathway.[72] Specific goal-directed transfusion can be achieved by using such algorithms, leading to a reduction of blood component used and to a possible better outcome by stopping bleeding in trauma early.

At our institution, we recently implemented a transfusion algorithm for massively bleeding patients (Figure 1). This algorithm incorporates information obtained from patient's history, clinical presentation, routine coagulation laboratory and bed-site viscoelastic coagulation testings. Interestingly, our experience implementing and adhering to a transfusion algorithm is in accordance with previous studies showing significant reduction in number of transfusion administered, decrease of blood loss and

costs [27,72,73]. For example, in the first 6 months after implementation of the algorithm, the use of FFP dropped by approximately 50% and RBC as well as platelet administration decreased by approximately 20% each. Despite a moderate increase in costs for point-of-care coagulation monitoring and more frequent administration of specific coagulation factor concentrates (fibrinogen, factor XIII, PCC, rFVIIa), we had a significant cost savings in this first 6 months after implementing our algorithm.

Adverse effects of transfusion

The administration of blood products is associated with adverse effects [74] including viral or bacterial [75] transmission. This is perceived to be under control in developed countries [76]. However, there are other issues. RBC transfusion has been found to be a highly significant and independent factor for an increased mortality and morbidity in a variety of surgical situations [77]. Also nosocomial infections are several fold more frequent in transfused vs. non-transfused patients.[45,78,79] Transfusion-related acute lung injury (TRALI) is another risk [80,81] occurring during or within 6 hours of transfusion [82]. The risk for TRALI is estimated to be 1 in 1000 to 1 in 4000 units transfused with a significant mortality [82]. Immune suppression or modulation potentially associated with multi organ failure (MOF) and an increased cancer recurrence is another adverse effect of allogeneic blood transfusions [83-85], particularly with long storage times.[86]

Differences between civilian and non civilian sector

In recent publications of the US military the use of fresh whole blood has been described for soldiers with life threatening injuries. Spinella found that surviving improved 48

hours and 30 days after whole blood transfusion compared to massive transfusion of stored red cells.[87,88] The risk of transmission of infectious agents and other microorganisms remains higher for fresh whole blood then RBCs. In the civilian sector such protocols thus are not applicable.

Trauma exsanguination protocols like the one of Cotton[89] try to create whole blood conditions by transfusion fix amounts of RBCs, FFP and platelets. However, this does not seem to be an adequate strategy in civilian trauma managment, the goal to achieve must be a specific management and replacement of blood components and factors according to on-line bed-side coagulation monitoring which may not be feasible in a military environment.

Conclusion

Kommentar [OMT6]: 50-100 Wörter, es sind73

Although a lot of progress has been made in the field of trauma patients, treatment of massive bleeding still remains an interdisciplinary challenge for surgeons and anesthesiologist. Modern and future transfusion strategies are based on on-line bed-side coagulation monitoring with specific goal-directed administration of anti-fibrinolytics, coagulation factors, RBC, fresh frozen plasma and platelets to optimize coagulation early. This allows improving patient's outcome, minimizing exposure to blood products and reducing costs.

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