An approach to transfusion and hemorrhage in trauma: current perspectives on restrictive transfusion strategies

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Hemorrhagic shock is a leading cause of death in trauma patients. Surgical control of bleeding and fluid resuscitation with both crystalloid and blood products remain the mainstay of therapy for injured patients with bleeding. However, there has been a recent re-evaluation of transfusion practice. Both the fear of transmissible disease and the costs of transfusing blood products have led to increasingly restrictive transfusion practices. A small percentage of trauma patients require massive transfusion. These patients are complex and difficult to manage, and clinicians must act quickly to save them. There is little evidence to help guide clinical transfusion decisions in these patients. A rational approach to using blood products requires an understanding of the end points of resuscitation. Resuscitation with fluids and red cells is necessary to improve perfusion and oxygen delivery to tissues. Avoiding overtransfusion is key, however, because transfusion is also associated with significant risks. This trend toward reducing allogenic blood exposure will likely continue. New technologies that have the potential of reducing blood loss and transfusion requirements in trauma patients with massive bleeding are being developed, and similar old technologies are being reapplied.

Le choc hémorragique est une cause importante de mortalité chez les patients traumatisés. Le contrôle chirurgical du saignement et la réanimation liquidienne au moyen de solutés cristalloïdes et de produits sanguins demeurent le principal traitement des patients traumatisés en hémorragie. On a toutefois réévalué récemment la pratique transfusionnelle. La crainte des maladies transmissibles et les coûts de transfusion de produits sanguins ont donné lieu à des pratiques transfusionnelles de plus en plus restrictives. Dans une faible proportion, les patients traumatisés ont besoin d'une transfusion massive. Ces patients présentent un cas complexe et difficile à gérer et les cliniciens doivent agir rapidement pour les sauver. Il existe peu de données probantes pour guider les décisions cliniques sur les transfusions chez ces patients. Une stratégie rationnelle d'utilisation des produits sanguins exige de bien comprendre les résultats décisifs de la réanimation. Il faut réanimer avec des liquides et des globules rouges pour améliorer la perfusion et l'alimentation en oxygène des tissus. La clé consiste à éviter la surtransfusion, car la transfusion entraîne aussi des risques importants. La tendance à la réduction de l'exposition au sang allogène se maintiendra probablement. On travaille à mettre au point de nouvelles techniques qui pourraient réduire la perte de sang et le besoin de transfusion chez les patients traumatisés victimes d'une hémorragie massive et on recommence à appliquer d'anciennes techniques semblables.

Hemorrhagic shock is the second most frequent cause of death in trauma patients and is the leading cause of early inhospital trauma deaths.[1] It develops when traumatic bleeding results in a pathophysiological state in which the circulatory system is unable to adequately perfuse tissues and meet oxygen demand. The main management strategies for treating hemorrhagic shock are the arrest of bleeding and the replacement of circulating volume and oxygen-carrying capacity.[2]

There is currently little debate about the need for restricting blood transfusions. The fear of transfusion-associated infections has been partly responsible for increasingly restrictive approaches.[3] Also, blood products remain a vital resource, and responsi-

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ble use of this limited commodity has been another reason for mandating judicious blood product use.[4] The challenge has been delineating appropriate triggers for blood use in trauma patients, without adversely affecting outcomes. We review the current literature on blood transfusions to develop a rational approach for using blood products in trauma patients.

Historical perspective

The benefits of whole blood transfusion for traumatic hemorrhagic shock became apparent during World War II.[5] With great foresight, British physicians established the infrastructure necessary to support a safe and efficient blood transfusion service, all before the start of hostilities. In contrast, American physicians and surgeons decided to rely solely on plasma to resuscitate injured solders. The futility of this plasma-only method was appreciated in North Africa, where significant numbers of American soldiers died from hemorrhage alone, compared with British soldiers. As a result, blood transfusions became an accepted part of American trauma doctrine.

In the postwar era, transfusion was considered relatively risk-free. Therefore, clinical standards for transfusion were very liberal, and one widely accepted trigger for red cell transfusion was a hemoglobin level below 100 g/L, irrespective of clinical status.[3] However, the discovery that blood transfusion could transmit HIV and hepatitis C virus (HCV) led to a re-evaluation of transfusion practices. Another reason for reexamining transfusion practices has been the increasing costs of transfusion. These costs per unit doubled from 1994 to 1995, because of the introduction of assays for numerous transmissible diseases.[4]

As a result, evidence-based recommendations have emerged to help guide clinicians in transfusing critically ill patients with anemia who are isovolemic and nonbleeding.[6] Trauma accounts for 13.4% of all blood products transfused in Ontario,[7] and these patients are often still actively bleeding and hypovolemic when transfusion therapy is considered. Also, 3% of trauma patients undergo massive transfusion (10 or more units); 50% of these develop an international normalized ratio (INR) > 2.0 and 33% have a thrombocytopenia with a platelet count below 50×10^9/L.[8] There are few recommendations to help clinicians with treatment decisions. Rationalizing transfusion practice in trauma patients with bleeding may reduce inappropriate transfusions — an estimated 33%–62% of all transfusions.[9]

Adverse effects of blood transfusion

Transfusion-related risks can be divided into transfusion-associated infections, immunological risks, metabolic complications and mistranfusion.

Infection

The most clinically significant viral infection remains hepatitis B, with a per unit risk of 1:82 000.[10] The risk is now 1:4.7 million for contracting HIV and 1:3.1 million for contracting HCV, per unit of transfused blood.[10] The risk from bacterial pathogens is higher, especially in trauma and intensive care unit (ICU) patients, who may be immunocompromised. The risk of sepsis from platelet transfusion is estimated to be approximately 1 in 10 000 and 1 in 100 000 from red cell transfusion.[11] Bacterial contamination of platelets is more common than red cells, because platelets must be stored at room temperature.

Immunological risks

There is also evidence that red cell transfusions are associated with an immunomodulatory effect, which is potentially harmful to trauma patients. Allogenic blood transfusions have been associated with a reduction of cell-mediated immunity,[12] which may lead to increased sepsis. Also, transfusion may have proinflammatory effects, which can lead to multiple organ failure.[13,14]

Metabolic complications

Metabolic complications from massive transfusion include hypothermia, acidosis and coagulopathy; we discuss these later. Hyperkalemia, hypocalcaemia and citrate toxicity also tend to occur in trauma patients with massive transfusion.[11]

Mistransfusion

Mistransfusion is estimated to occur in 1:40 000 transfusions and is defined as an ABO-incompatible reaction owing to an error.[11] Mistransfusion is a leading cause of morbidity and mortality from transfusion, because it can lead to a major hemolytic reaction.[11] Non-ABO acute hemolytic reactions and febrile nonhemolytic reactions are much more common but are generally mild and self-limiting in nature.

Acute management of hemorrhagic shock

General principles

The accepted principles of managing hemorrhagic shock are suggested by the accuracy of the advanced trauma life support (ATLS) guidelines.[2] Airway and breathing issues have priority over bleeding because of their acuity. The treatment of airway and breathing problems may sometimes improve the "shock state" by improving oxygenation. Tension pneumothorax, a mechanical cause of shock, may also be identified and treated in this phase. See Figure 1 for our institutional guidelines for resuscitation.

Volume resuscitation versus control of hemorrhage

After airway and breathing, ATLS

mandates an assessment of circulatory status. Patients with signs and symptoms of inadequate tissue perfusion are presumed to be in hemorrhagic shock.[2] ATLS then advocates 2 interventions: control of hemorrhage and reversal of hypovolemia. There is controversy over which should be corrected and with what solution.[15]

"Permissive hypotension" is a fluid resuscitation strategy that advocates withholding fluid and red cell products until after surgical control of bleeding is achieved. The raised hydrostatic pressure from volume

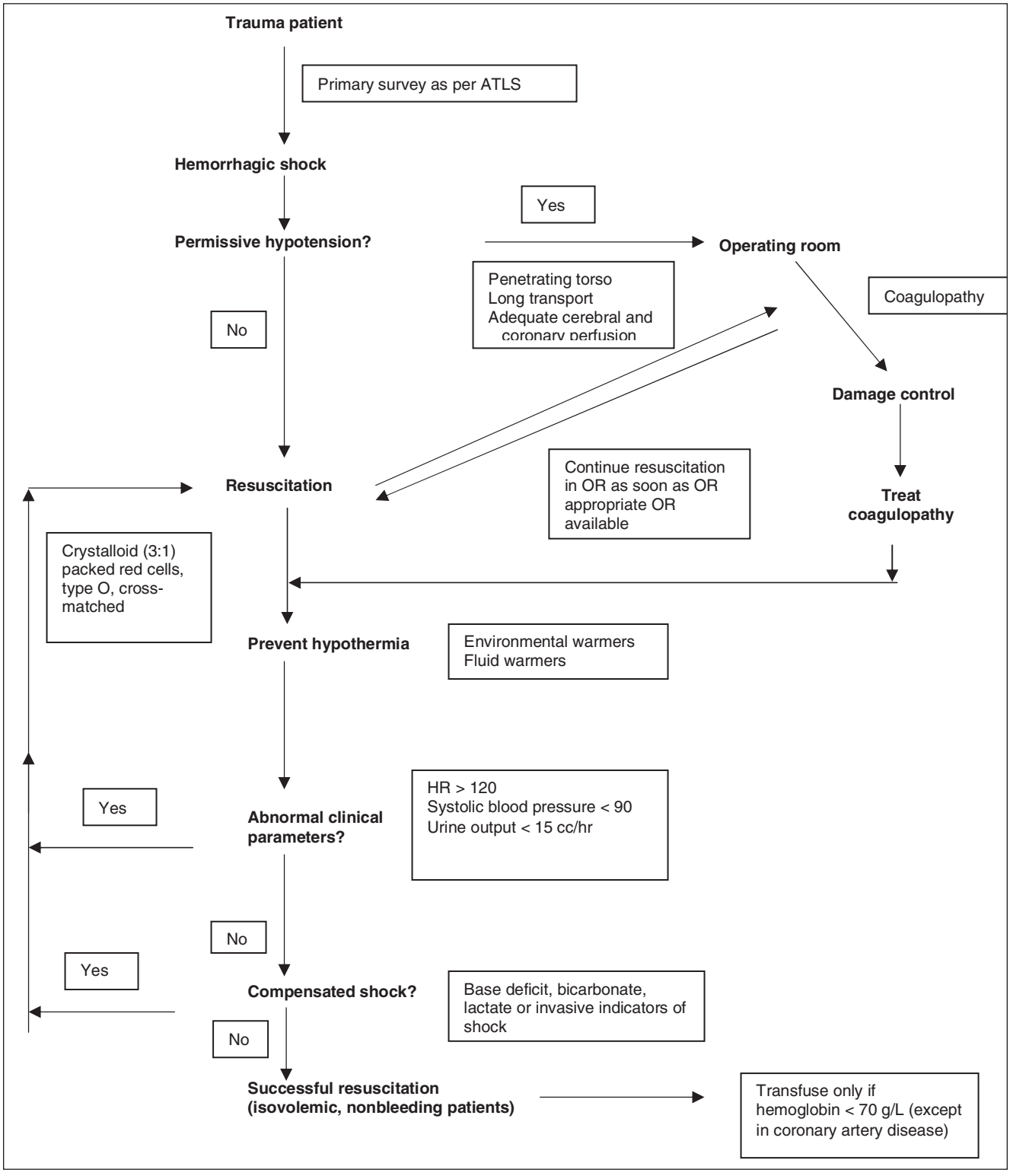

FIG. 1. Institutional guidelines for resuscitating hemorrhagic shock.

replacement may lead to increased blood loss. A prospective randomized trial was conducted in patients with penetrating torso trauma and signs of shock.[16] Mortality was reduced in the delayed-fluid resuscitation group, although time delays to surgery were actually increased.

Our institution now advocates "permissive hypotension," in the context of penetrating torso trauma. Patients who require prolonged transport may still require fluid and red cell resuscitation to maintain cerebral and coronary perfusion. Vigorous volume replacement is still appropriate in patients with blunt injury, because brain injury commonly complicates blunt trauma and hypotension further increases the risk of death for patients with brain injury.[17]

Volume resuscitation

In adult hypotensive patients, ATLS calls for a rapid infusion of 2 L of an isotonic crystalloid solution. A second bolus is appropriate if there is no response or if there is only a transient response. Red cell transfusions are recommended for transient or initial nonresponders.[2]

At our institution, we transfuse crossmatched blood if the patient's clinical status permits the 45-minute wait for the full cross-matching process. If the situation is emergent, we try to use group-specific blood where possible, to avoid depleting our type-O stock. Transfusing type-specific blood has been shown to be safe in trauma situations and avoids the transfusion of significant anti-A and anti-B antibodies from the residual plasma in packed red cell units.[18,19] As a last resort, we use type O– blood in young women and type O+ in all other patients, when uncrossmatched blood is required.

Red cell salvage (autotransfusion) is another strategy developed to reduce exposure to allogenic blood and refers to when the patient's own lost blood is collected and then reinfused. A systematic review of the literature suggests that autotransfusion reduces transfusion in elective surgery[20]; however, there is no evidence to support its use in trauma. One potential disadvantage for trauma patients is the possible development of coagulopathy from the anticoagulant, which is used in the cell salvage process.[21] This may be only a theoretical risk; a meta-analysis of 27 studies revealed no increase in adverse events in treatment (cell salvage) groups.[22]

End points of resuscitation

ATLS cautions against using hemoglobin level as a guide for resuscitation. Hemoglobin level is known to be inaccurate while active hemorrhage is still occurring, because it might have not yet equilibrated with the total circulating plasma volume.[2] We try to keep a minimum hemoglobin level of above 70 g/L during this resuscitative phase. There is evidence that profound anemia itself can contribute to coagulopathy.[23,24]

The primary goal of transfusing red cells is to enhance tissue perfusion and oxygen delivery.[2] Therefore, during active hemorrhage, red cell transfusions should primarily be guided by the rate of ongoing bleeding and by signs and symptoms of inadequate tissue perfusion. Traditional clinical signs of shock include a heart rate of over 120 beats/minute, a systolic blood pressure less than 90 mm Hg or a urine output of less than 15 mL/hour.[2] Fluid resuscitation with crystalloid and blood products is obviously still required when these parameters are abnormal. However, even after normalization, up to 85% of patients with severe injury have other biochemical evidence of inadequate tissue oxygenation.[25] This condition is termed compensated shock. Recognition and reversal of this state can minimize the risk of death and subsequent development of multiple organ failure.[25]

In addition to monitoring heart rate, blood pressure and urine output, the Eastern Association for the Surgery of Trauma (EAST) recommends using several different laboratory measures of persistent metabolic acidosis — base deficit, bicarbonate, and lactate — to detect this compensated shock state, after hemodynamic parameters are normalized and bleeding is controlled.[25] The basis for these tests is the observation that the body compensates for inadequate tissue oxygenation with anaerobic glycolysis. Therefore, the laboratory evidence of additional extracellular acidity can help quantify the magnitude of shock.

At our institution, after bleeding has been controlled and hemodynamics are normalized, we sample arterial blood for base deficit and analyze venous blood for lactate. A persistent base deficit or elevated lactate suggests ongoing resuscitation requirements. Further, Davis and others[26] showed that base deficit values could reliably predict the volume of additional fluid and blood requirements in these patients.

Other tests have been shown to be useful as end points for resuscitation. EAST suggests the use of gastric mucosal pH testing and measuring right ventricular end-diastolic volume index (RVEDVI) to monitor resuscitation. In addition, the American Society of Anesthesiologists advocates using global indicators of inadequate tissue oxygenation. Oxygen extraction (> 50%), partial pressure of mixed venous oxygen (< 25 mm Hg) and mixed venous oxygen saturation (< 50%) have all been proposed as potential red-cell transfusion triggers.[27] Because these tests are more difficult to obtain and more complex to interpret, we limit their use to cases where base deficit and lactate values are unreliable.

Control of hemorrhage

Massive hemorrhage after traumatic injury is frequently a combination of surgical and coagulopathic bleeding. Surgical bleeds originate from lacerated vessels at the site of injury. In

contrast, coagulopathy results from a complex, multifactorial process and commonly develops after severe injury. Prompt control of hemorrhage to avoid massive transfusion is the *sine qua non* of treatment for hemorrhagic shock.

Surgical hemorrhage

In patients with hemorrhagic shock, the site of bleeding must be rapidly identified as part of the primary survey. Major sites of internal hemorrhage include the chest, abdomen, extraperitoneal pelvis and peri-femoral muscle compartments. Frequently overlooked external sites include lacerations of the scalp and soft tissue. Usually, surgical control involves ligation of the bleeding vessels; however, angiographic embolization is increasingly being used as a minimally invasive technique for control of hemorrhage, particularly for hemorrhage from pelvic fractures.[2]

Coagulopathy

Coagulopathy develops in 44% of all seriously injured patients[8] and accounts for most deaths that occur in the first 24 hours of admission after trauma.[28] Coagulopathic patients can consume massive amounts of blood products. Rationalizing therapy for these patients can potentially improve outcomes and reduce transfusions.

The mechanism of coagulopathy is multifactorial. Postinjury, the predominant factor is core hypothermia. Hypothermia adversely affects platelet function, particularly when the core temperature falls below 34°C.[29] Other well-described factors that contribute to coagulopathy include metabolic acidosis from inadequate tissue oxygenation and the dilutional effects of massive transfusion (> 1 blood volume, or approximately 5 L in a 70 kg adult) on clotting factors and platelets.[29] Other pathophysiological events include hyperfibrinolysis and consumption coagulopathy, although the associations are less clear.[30] Therapy for coagulopathic patients requires the replacement of lost clotting components and correction of predisposing factors.

Platelets

Platelets are crucial to the clotting process by forming a platelet plug. Ultimately, fibrin stabilizes this plug. Bleeding is unlikely to be aggravated by thrombocytopenia when the platelet count is greater than 50 000/μL.[27,31,32] Maintaining a platelet count above 100 000 μL has been recommended if head injury is present.[33] See Table 1 for guidelines for using component therapy in patients with massive transfusion.

Fresh frozen plasma (FFP)

Appropriate coagulation requires a minimum concentration of clotting factors that is 20%–30% of normal. Replacement of 1 blood volume reduces the original concentration of clotting factors to one-third. Four units of FFP (10–15 mL/kg) is the calculated dose that will raise the concentration of blood clotting factors to 30% of normal. We advocate transfusing 4 units of FFP at a time.[32] See Table 1.

Cryoprecipitate

In trauma patients, cryoprecipitate is used to replace fibrinogen and isindicated for levels less than 1.0 g/L.[32] Cryoprecipitate administration results in high donor exposure, owing to the large number of donors per pool.[32]

Correction of factors leading to coagulopathy

To prevent coagulopathy, aggressive measures should be taken in all pa-

Table 1

Sunnybrook recommendations for blood component therapy in coagulopathic trauma patients

Blood product	Recommendation	Considerations	Suggestion
FFP	Active bleeding and PT/PTT more than 1.5 × normal. Microvascular bleeding or massive transfusion and deteriorating status. Emergent reversal of warfarin.	Consider patient's clinical status and transfuse empirically if it precludes waiting 30–45 min for PT/PTT results. Give vitamin K to reverse warfarin effect.	Transfuse 10–15 mL/kg (3–4 units).
CRYO	Ongoing bleeding in patients with fibrinogen concentration < 0.8–1.0 g/L.	Consider patient's clinical status and transfuse empirically in setting of massive transfusion and if it precludes waiting for fibrinogen results; each dose should increase fibrinogen by 0.5 g/L.	Transfuse 1 unit/10 kg (8–12 units/dose).
PLT (× 10^9/L)	Ongoing blood loss and PLT < 50. Head trauma and PLT < 100. Active bleeding and PLT dysfunction (ASA, bypass, hypothermia).	Consider etiology of thrombo-cytopenia.	Transfuse 1 pool random donor platelets or 1 unit of apheresis platelets.

FFP = fresh frozen plasma; PT = prothrombin time ; PPT = partial thromboplastin time; CRYO = cryoprecipitate; PLT = platelets; ASA = American Society of Anaesthesiologists.

tients with severe injury[29] (see Fig. 1). Recognition and treatment of shock is necessary to minimize metabolic acidosis. Also, as previously discussed, appropriate therapy of coagulopathy with blood products should be instituted. Most importantly, hypothermia should be aggressively treated and prevented. Use of environmental and fluid warmers should be routine and should be used as soon as possible in unstable patients with bleeding. Its use should be instituted after the transfusion of the sixth unit of blood product in otherwise stable patients.[11]

"Damage control" surgery

Despite these efforts, hemorrhage is still the leading cause of inhospital deaths during the first 24 hours after admission.[28] As a result, "damage control" surgical techniques have been advocated to reduce operative time and allow for early transport to the ICU. The principle behind damage control surgery is that immediate organ repairs may be detrimental. Staged operations allow for rewarming and resuscitation and can potentially interrupt the cycle of massive transfusion, hypothermia, acidosis and coagulopathy that leads to further bleeding and sometimes death.[28] The 3 stages of damage control surgery are limited operation for control of hemorrhage and contamination, with packing of potential spaces; resuscitation in the ICU; and reoperation for definitive repairs and completion of gastrointestinal anastomoses. Preliminary evidence suggests that damage control techniques can reduce bleeding, reduce blood transfusions and improve survival.

Controversies

One concept has emerged strong and deserves comment. It relates to the management of trauma patients with massive bleeding and coagulopathy. Based mostly on the military experience emerging from the Iraq and Afghanistan wars but also from civilian clinical practice reviews and an International Consensus Conference, it has been proposed that coagulopathic trauma patients be primarily resuscitated with thawed FFP in a ratio of 1:1:1 to red blood cells and platelets, virtually receiving "reconstituted whole blood."[34]

Transfusion in resuscitated, nonbleeding patients

Only after patients are appropriately resuscitated and bleeding is controlled, there is good evidence to recommend a restrictive transfusion strategy. Hebert and colleagues[35] conducted a multicentre, randomized controlled trial that compared the use of restrictive and liberal strategies for allogenic red cell transfusion in isovolemic, nonbleeding ICU patients. Inhospital mortality was significantly reduced in patients transfused for hemoglobin levels below 70 g/L, compared with those transfused for levels below 100 g/L. The greatest mortality benefit was seen in young (aged < 55 years) patients who were less severely ill (Apache II scores < 20). Thus, we use a transfusion trigger of 70 g/L in patients without shock or significant cardiac disease. In cardiac patients, we still guide our transfusion practices by estimating oxygen delivery.

Emerging technologies for reducing blood use

Better end points to guide transfusions

One potential method for reducing blood transfusion is thromboelastography (TEG). TEG rapidly assesses the coagulation cascade, starting from the initial platelet–fibrin interaction through to clot lysis.[29] Although the use of TEG has not been proven in trauma patients, it has been shown to reduce the allogenic blood exposure in the elective cardiac surgery setting.[36] Both FFP and platelet use was diminished with the use of TEG, with no adverse effects on blood loss or on rates of reoperation for bleeding.

Fibrin sealants

Fibrin sealants mix thrombin and fibrinogen as a means of accelerating the formation of the fibrin clot. A systematic review of trials found that fibrin sealants reduce surgical blood loss and the need for blood transfusion in elective surgery.[37] Considering the need for a dry surface, the current sealants are of little use in trauma; however, studies in animal models suggest that fibrin sealants might have a role in traumatic hemorrhage.[38]

Antifibrinolytics

Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce surgical blood loss. Based on their positive results in elective surgery, antifibrinolytics are attractive drugs for treating coagulopathy in trauma patients, but they require well-designed prospective studies to delineate their use in this setting.[39]

Recombinant factor VIIa

Recombinant activated factor VIIa (rFVIIa) has been approved for hemophilia patients with inhibitors. Recently, it has been used off-label as a hemostatic agent in trauma patients with massive bleeding. Boffard and colleagues[40] have published their results of a multicentre double-blind, randomized controlled trial on rFVIIa use in these patients. In blunt trauma patients surviving 48 hours or more, red cell transfusions were significantly reduced by the use of rFVIIa, relative to placebo. Similar but less-significant trends were observed in penetrating trauma. Also, trends toward a reduction in mortality and critical complications were observed. Adverse events including thromboembolic events

were evenly distributed between groups. We advocate the use of rFVIIa as an adjunct to surgical control of hemorrhage in patients with massive bleeding, after 8 units of red cells have been transfused and if there is still evidence of marked, ongoing bleeding.

Artificial hemoglobin-based oxygen carriers

Investigators have developed cell-free hemoglobin solutions, where red cell membranes are removed from outdated red cells and the hemoglobin molecules are cross-linked to prolong shelf-life.[21] Many of these products are currently in phase III testing, in large prospective prehospital trauma and elective surgery studies. These products hold the promise of being able to improve oxygen delivery to tissues, without the same risks for infectious, immunological and metabolic complications as allogenic blood transfusions.

Summary

Trauma patients with massive bleeding are complex and difficult to manage, and clinicians often have little time to decide on their course of action.

A rational approach to using blood products in patients with bleeding requires an understanding of the principles of managing hemorrhagic shock. The main priorities are controlling hemorrhage and restoring adequate oxygen delivery to tissues. Surgical control and treatment of coagulopathy are required to stop hemorrhage in these patients. Resuscitation with fluids and red cells are necessary to improve perfusion and oxygen delivery to tissues. However, avoidance of overtransfusion is key because transfusion is also associated with significant risks.

Once patients are resuscitated and further bleeding is stopped, use of conservative transfusion triggers is recommended to avoid excessive transfusion and bad outcomes. Avoiding overzealous venipuncture (for complete blood counts) can also prevent worsening anemia in this phase. The trend toward reducing allogenic blood exposure will likely continue. New pathogens continue to emerge to challenge existing safety measures. Fortunately, new technologies are being developed that have the potential of reducing blood loss and transfusion requirements in trauma patients with massive bleeding.

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