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Transfusion Goals and Hemostatic Management of the Anticoagulated Trauma Patient: Can You Plug a Hole in the Dam?

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Stem Case and Key Questions Content

Case Description, Part 1

67 year old male presents for emergency evacuation of an acute traumatic subdural hematoma. The patient was brought to the emergency room by EMS after sustaining a fall on the ice. On exam the patient is lethargic but without focal neurologic deficits. He is not oriented enough to provide a full history, but the EMTs report a vague history cardiovascular disease from his neighbor who witnessed the fall and claims the patient suffers from “heart problems.”
The patient’s admission labs are significant for hemoglobin of 8.6, hematocrit of 26.1 and platelets of 194. A standard chemistry panel was within normal limits; the coagulation profile remains pending. He is currently hemodynamically stable with blood pressure of 124/68 and heart rate of 97; he has an adequate cough and gag reflex to protect his airway despite lethargy. He is transferred to the intensive care unit for further stabilization and management.

Key Questions, Part 1

On arrival to the ICU the neurosurgeon evaluating the patient for possible decompressive craniectomy suggests transfusion. How would you respond? And would your transfusion threshold be different if the patient did not have cardiovascular disease?
The surgeon also requests that the patient receive fresh frozen plasma and platelets. What are the risks associated with transfusing packed red blood cells vs. plasma and platelets? Given that this patient sustained traumatic injury, are there specific transfusion goals to manage hemostasis?

Case Description, Part 2

The patient’s spouse becomes available for questions concerning his medical history and medication regimen. He has mild coronary artery disease medically managed with aspirin, atorvastatin, and metoprolol. He is reportedly asymptomatic with moderate exercise. He has paroxysmal atrial fibrillation on full anticoagulation with dabigatran (Pradaxa).

Key Questions, Part 2

The patient’s wife expresses concern for the risks of blood transfusion and asks about alternatives to transfusion or methods to reduce the risk of further blood loss. She is also concerned that the patient is on “blood thinners” and wants to know if there is any antidote to reverse the effects of dabigatran. The neurosurgical service wants to use fresh frozen plasma because they have used this in the past for reversal of warfarin therapy. What are the current guidelines for reversal of warfarin therapy for urgent procedures vs. hemorrhagic emergencies?

Model Discussion Content

Model Discussion. Part 1

1. ASA guidelines for transfusion.

There are few guidelines available for specific transfusion triggers especially for the perioperative patient. The ASA Practice Guidelines for Blood Component Therapy recommend transfusing red blood cells for hemoglobin levels less than 6 g/dL. Furthermore, they state that it is reasonable to transfuse to a goal hemoglobin > 7 g/dL, but it is rarely necessary to transfuse over 10 g/dL. For all values from 7-10 g/dL, the ASA task force suggests transfusion should be guided by the patient's clinical situation including evaluation of ongoing bleeding, and evidence of end-organ hypoxia or dysfunction (metabolic acidosis, oligouria, mental status changes, or evidence of myocardial ischemia).1 Our patient is normotensive and mildly tachycardic. Further investigation for evidence of tissue hypoxia such as ECG changes consistent with ischemia, or oligouria despite adequate blood pressure, or hypovolemic shock, would assist in the decision to transfuse him, or if he had ongoing bleeding from his traumatic injury.

Recent guidelines from the British Journal of Haematology also recommend a restrictive transfusion practice for hemodynamically stable but critically ill patients.2 However they suggest a higher transfusion threshold for patients with neurocritical illness. The new evidence based guidelines for those suffering from traumatic brain injury (TBI) suggest goal hemoglobin of 7-9 g/dL, however patients with severe TBI and evidence of cerebral ischemia should maintain hemoglobin over 9.0 g/dL. Furthermore the AABB recommends a transfusion threshold of > 8.0 g/dL for perioperative patients or those with signs of active bleeding.3

There are several studies to support the increased morbidity and mortality associated with perioperative blood product transfusion; the land breaking article to document the non-inferiority of restrictive transfusion practices was the Transfusion Requirements in Critical Care (TRICC) trial from 1999 where euvolemic, hemodynamically stable critically ill patients were randomized to a restrictive arm (goal hemoglobin level > 7 g/dL) or a liberal group (hemoglobin goal > 10 g/dL). There was no significant difference in outcomes for the two groups and actually younger patients with less acute illness in the liberal transfusion group had a higher morbidity and mortality.4 However, these results are not generalizable to the bleeding perioperative patient with a traumatic brain injury.

Hemoglobin is the main oxygen carrier within the blood and plays an integral role in oxygen delivery (DO2 = Cardiac Output x Oxygen Content of the blood). Therefore, if the hemoglobin falls to a critical value, oxygen carrying capacity becomes deficient and tissue hypoxia ensures resulting in end-organ ischemia and hemorrhagic shock. The body has several inherent compensatory mechanisms for acute anemia the most important of which is to increase cardiac output. In addition, the tissues respond to hypoxia and acidosis with arteriole vasodilation and changes in the microcirulatory blood flow and oxygen extraction. Lastly, acidosis and locally released 2,3-diphosphoglycerate (DPG) from erythrocytes result in a rightward shift of the oxygen dissociation curve to improve the offloading of oxygen from hemoglobin at the tissues. This patient has just suffered an acute injury and it is important to remember that in the setting of acute hemorrhage, trauma, or critical surgical bleeding, the hemoglobin level may be deceivingly high prior to volume resuscitation. There is little evidence for guidance on transfusion thresholds during hemorrhagic shock, however regardless of the initial hemoglobin concentration, blood product transfusion should be initiated in a patient with class II

hemorrhagic shock (blood loss of > 15-30% of estimated blood volume) with preexisting cardiovascular disease, acute neurologic injury and or preexisting anemia, and in patients with class III to IV hemorrhagic shock with estimated losses in excess of 30% total blood volume.5
2. Origins of higher hemoglobin threshold for CV disease.

Traditional transfusion practices endorsed higher hemoglobin goals for patients with cardiovascular disease given their lack of ability to increase cardiac output in response to acute anemia. However, these recommendations were based on poorly controlled retrospective data that showed an association between anemia in patients with acute coronary syndrome and mortality. There was no evidence to support the conclusion that transfused red blood cells could reverse the mortality risk of acute anemia. Several subsequent review articles and meta-analysis have since supported the morbidity risk associated with unnecessary blood product transfusion and the non-inferiority of restrictive transfusion practices for patients despite significant cardiovascular disease. Recently the AABB released guidelines for transfusion threshold in patient with active cardiovascular disease which state that practitioners may maintain a restrictive transfusion threshold of 7-9 g/dL and > 8.0 g/dL in patients who are symptomatic or demonstrating evidence of organ ischemia; these guidelines are also consistent with those published in the British Journal of Haematology.2,3

The Transfusion Requirements After Cardiac Surgery (TRACs) trial was a randomized controlled trial of post cardiac surgery patients comparing a restrictive transfusion strategy with goal hematocrit > 24% to patients with transfusion threshold of hematocrit > 30%. Again, the liberal transfusion protocol was an independent predictor for morbidity and mortality.6 This trial is the main evidence to support the most recent update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologist Blood Conservation Clinical Practice Guidelines which recommends hemoglobin goals over 7 g/dL with transfusion of red cells indicated for “critical noncardiac end-organ ischemia,” or ongoing blood loss.7

Our patient has a vague history of cardiovascular disease, however outside of the setting of acute coronary syndrome and without evidence of acute myocardial ischemia, his history alone should not alter his transfusion threshold.

3. The complications of transfusion with blood component therapy can be classified as infectious or non-infections and further by immune mediated reactions vs. non-immune mediated reactions.

Transfusion Transmitted Infections8:
Viral infections are becoming less and less frequent as a result of the advanced screening of the blood supply with nucleic acid testing thereby decreasing the window period for detecting a new infection in blood donors. Cytomegalovirus (CMV) remains the most common transfusion transmitted infection with a rate of 1-3% incidence per donation. However, CMV remains asymptomatic in most immunocompetent patients and can be avoided with leukoreduction of blood components prior to transfusion. The residual risk of transfusion transmitted Hepatitis B remains high (1/360000 donations) secondary to the high population prevalence and long window period for serologic detection in donors. On the contrary, the risk of transfusion transmission for Hepatitis C and HIV exceed 1/1.6 million and 1/1.8 million respectively. Bacterial contamination of blood product components carries an incidence of 1/3000 units for all products with multidonor platelet packs carrying the highest risk secondary to storage at higher

temperatures (20-24 °C) and multiple venipunctures per dose. Vigilance for bacteremia and sepsis after transfusion should remain high.
Emerging infections are extremely rare but may include epidemic viruses such as West Nile virus or locally prevalent infections such as Dengue virus, Chagas, Malaria, or Creutzfeldt-Jakob disease.

Non-infectious Transfusion Reactions9:
Immune-mediated reactions range from simple fever, utricaria, allergy and anaphylaxis, to acute and delayed hemolysis, alloimmunization, transfusion related acute lung injury, graft versus host disease, and the broad concept of transfusion related immunomodulation. These reactions have variable clinical presentations and carry different risks of morbidity and mortality depending on the patient's comorbidities including baseline immunosuppression and cardiopulmonary function.

Transfusion related acute lung injury (TRALI) occurs in approximately 1 out of every 1000 blood product transfusions. The mechanism of injury is not known with certainly but likely involves multifactorial insults commonly referred to as the "Two-hit hypothesis." The first insult stems from the patient's acute illness, surgery, or trauma which "primes" the immune system resulting in activated neutrophils being deposited on the endothelial lining of lung tissue. These neutrophils become activated by the inflammatory mediators infused via stored blood products (lipopolysaccharides, free radicals, interleukins, and lipid degradation products) or from antibodies from the donor that complex with recipient antigens thereby initiating complement activation. This immune activation may then result in endothelial breakdown with a breach of the capillary membrane and subsequent pulmonary edema. Given this presumed mechanism of injury, blood components that contain plasma are associated with the highest risk of TRALI. The clinical presentation of TRALI is acute and diffuse non-cardiogenic pulmonary edema. Treatment focuses on supportive care.

Transfusion related immunomodulation (TRIM) is not a new concept with blood component therapy; however it is gaining appreciation as a possible contributor to post-transfusion morbidity. The proposed mechanism for TRIM is complex and controversial, but stipulates the initiation of a pro-inflammatory state while depressing protective systemic immune mechanisms. The question of whether or not leukoreduction can mediate the risk of TRIM remains under investigation.

Non-immune mediated reactions related to patient comorbidities or transfusion practice include transfusion associated cardiovascular overload (TACO), hypothermia, hyperkalemia, and hypocalcemia associated with rapid and massive transfusions. Measures for warming the blood should be taken with the highest vigilance, as well as supportive care and active management of dilutional coagulopathy, electrolyte disturbances, and acidosis.

4. Transfusion management for trauma
The question remains of whether this patient's transfusion management strategy should include empiric transfusion of plasma and platelets prior to the availability of coagulation test results. Over the past decade there has been growing attention to the management of dilutional coagulopathy associated with massive transfusion and hemorrhagic shock. Traditionally trauma patients were resuscitated with packed red blood cells and isotonic crystalloid, followed by directed blood component therapy based on the results of coagulation tests. This style of

management introduces a significant delay in the treatment of coagulopathy associated with hemorrhagic shock given the need to wait for laboratory results before ordering, thawing and administering plasma or platelets. Consequently the current strategy in many trauma centers involves a near one to one ratio of packed red blood cells to plasma. Several reviews show improved survival with ratios of red cells to plasma greater than 3:2. However many of these studies were retrospective and are flawed by "survivor bias." The few randomized controlled trials available have yet to show definitive outcome benefits.10

Model Discussion. Part 2

5. Intraoperative blood sparing techniques

Given the significant risks associated with blood product transfusion, all reasonable low risk methods for blood conservation should be utilized to their highest potential. Intraoperative cell salvage systems are often employed for elective high risk surgery when blood loss is anticipated to exceed 1500 mls. These systems are rather simple to assemble and can be used for emergency surgeries, trauma, and even in the middle of an ongoing operation when blood loss exceeds what was expected.

You could also inform the patient's wife that there are pharmacologic adjuvants for hemostasis including antifibrinolytics and 1-deamino-8-D-arginine vasopressin (DDAVP) have both been shown to decrease critical bleeding especially for traumatic hemorrhage. The CRASH 2 randomized controlled trial of over 20,000 trauma patients documented a substantial mortality reduction with the use of lysine analog antifibrinolytics including tranexamic acid and ε-aminocaproic acid.11 DDAVP functions to improve primary hemostasis by up regulating the release of von Willebrand factor from coagulation factor VIII thereby improving platelet adhesion, activation, and aggregation. Both of these agents are rarely associated with any significant side effects but may increase the risk of hyponatremia (DDAVP) and thromboembolism.

6. Mechanism of action and pharmacodynamics/pharmacokinetics of new oral anticoagulants

Dabigartran (Pradaxa) is a direct thrombin inhibitor and classified along with, direct acting factor Xa inhibitors, rivaroxiban and apixaban, as part of a new class of oral anticoagulants commonly used place of warfarin for stroke prophylaxis and prevention of venous thromboembolism. These agents have a wide therapeutic window, no food or drug interactions, little inter-individual variability, and rapid onset of action making them much easier to manage than warfarin. Effect monitoring is unnecessary with dosing regimens that are simple and universal.
However, unlike warfarin, there is currently no antidote or reversal agent, and no coagulation test for bleeding risk. This complicates the management of patients undergoing surgery, urgent procedures, and those with hemorrhagic emergencies. Given the mechanism of antagonism for thrombin and factor X, theoretically TEG may provide some guidance for the anticoagulation effects, but this is unstudied in the literature. Furthermore, the best reversal agents currently available are prothrombin complex concentrates (PCCs). These concentrates vary in their composition, but commonly contain factors II (thrombin), VII, IX, and X. These concentrates are inactive and generally complexed with an anticoagulant (antithrombin or heparin), thereby limiting the risk of thromboembolism. If PCCs are not available, FFP is considered a second line therapy for reversal.12

7. Discuss the options for reversal of warfarin therapy for urgent procedures and emergencies

The recommendations for warfarin reversal depend on the patient's symptoms and the state of

urgency. Warfarin works by inhibiting the production of vitamin K dependent clotting factors, II, VII, IX and X; the most logical and appropriate reversal agent is replacement of vitamin K. Patients presenting with high INR and non-major bleeding should be reversed with 1-3 mg of intravenous vitamin K; this usually corrects the INR within 6 to8 hrs. Emergency reversal for patients with hemorrhage or those who require immediate surgery can be achieved with a 25-50 u/kg dose of PCCs. The half-life of most PCCs is short, and vitamin K should be given simultaneously for sustained results. Historically emergent reversal of warfarin was achieved with FFP; however this requires large volumes of transfusion (10-15 ml/kg) and provides unreliable results. Recombinant activated factor VII (NovoSeven, rFVIIa) has also been used to reverse warfarin, but the supporting literature was retrospective and although it reliably corrects the INR, it does not consistently correct clinical bleeding likely secondary to the ongoing inhibition of other vitamin K dependent clotting factors. Consequently, the current guidelines recommend the use of FFP when PCCs are not available.12

References

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