AACC CLINICAL CHEMISTRY TRAINEE COUNCIL

Pearls of Laboratory Medicine
www.traineecouncil.org

TITLE: Massive Transfusion

PRESENTER: Kerry O'Brien, MD

Slide 1
Hello, my name is Kerry O'Brien. I am the Associate Medical Director of the Blood Bank at Beth Israel Deaconess Medical Center in Boston, MA. I am also an Instructor in Pathology at Harvard Medical School. Welcome to this Pearl of Laboratory Medicine on "Massive Transfusion."

Slide 2:
The objectives for my presentation include: a discussion on the various definitions of massive transfusion, a discussion of the various clinical settings in which massive transfusions may occur, an explanation of the pathophysiologic changes involved in massive transfusion of blood products, and a discussion of protocols for managing blood products in a massive transfusion scenario.

Slide 3:
Several definitions of what constitutes a "massive transfusion" exist in the literature. Three widely accepted definitions include: the administration of greater than 10 red blood cell units to an adult patient in less than 24 hours; the replacement of more than 50% of the circulating blood volume of a patient within 3 hours; and the acute administration of 4-5 red blood cell units in 1 hour.

Slide 4:
Patients experiencing massive transfusion may present in various clinical circumstances. These patients may be trauma victims from motor vehicle accidents, recipients of blunt versus penetrating injury, and falls. Common diagnoses also include upper and/or lower gastrointestinal bleeds. Patients undergoing (or post-op from) vascular, cardiovascular, and neurosurgical procedures may also experience rapid major blood loss. Additionally, obstetric patients may require massive transfusion, most commonly due to post-partum hemorrhage from uterine atony.

Slide 5:
Patients receiving massive transfusion of blood products may experience numerous pathophysiologic changes as a result of blood product replacement as well as effects specific to the etiology of their bleeding. These changes include: early trauma induced coagulopathy, dilution coagulopathy, acidosis from tissue hypoperfusion and ischemia, hypocalcemia from

citrated blood products, and hypothermia from environmental effects as well as refrigerated blood products.

Slide 6:
Early trauma induced coagulopathy (ETIC), also known as the acute coagulopathy of trauma, was historically thought to be due to crystalloid and RBC administration without the administration of platelets, plasma, or both. Subsequent adult and pediatric studies showed that ETIC was present in 24% and up to 56% of severely injured patients, usually within 30 minutes of injury, even before receiving fluid and blood product resuscitation. ETIC is associated with systemic anticoagulation and hyperfibrinolysis. Tissue factor released following tissue injury from trauma or surgery activates coagulation pathways. The activation of the coagulation pathways results in a massive consumptive coagulopathy which is seen most prominently in patients with severe brain injury and extensive muscle damage (due to the large amount of tissue factor released).

Slide 7:
Infusion of massive amounts of crystalloids such as normal saline or lactated ringers prior to the transfusion of blood products can induce a dilutional coagulopathy in the massively bleeding patient. In addition, transfusion of red blood cells without platelets or the coagulation factors in plasma and cryoprecipitate can also produce or worsen a preexisting coagulopathy.

Slide 8:
Tissue hypoperfusion, exposure to citrate anticoagulation, and ischemia may lead to an acidotic state in the massively transfused patient. The decreasing pH impairs the function of the plasma proteases and may lead to increased degradation of fibrinogen. All of these effects worsen the already present coagulopathy.

Slide 9:
Hypocalcemia or decreased ionized calcium often occurs in the massively transfused patient as a result of citrate exposure. Citrate is used as the anticoagulant in the vast majority of stored blood products in the world. Citrate chelates calcium and in the massively transfused patient, this may result in a significant decrease in ionized calcium. This alteration in ionized calcium may lead to decreased cardiac contractility, arrhythmias, low cardiac output, and hypotension.

Slide 10:
While platelets are stored at room temperature (20-24°C), packed red blood cells and thawed plasma are stored between 1 and 6°C. Hypothermia can result in inhibition of coagulation protease pathway activity as well as platelet function. Hypothermia is common in many patients from environmental exposure, reduced heat production from hypoperfused muscles, exposed body cavities during surgery, as well as infusion of cold intravenous fluids including blood products during resuscitation. Blood warmers should be used, if at all possible, when rapidly transfusing massive amounts of blood products to reduce this risk.

Slide 11:

Massive transfusion protocols have been shown to improve patient survival. Currently the “ideal” ratio of red blood cells to plasma to platelets is a topic of debate in the transfusion medicine community. The oft-touted 1:1:1 ratio is based on retrospective data collected from war-time American combat hospitals involving mostly penetrating trauma patients. However, this data was subject to survivor bias, whereupon less injured individuals who survived longer than others were alive to receive more plasma and platelets than sicker, more injured patients who died prior to receipt of non-RBC products. In addition, there is the question of how applicable data from combat injured trauma patients is compared to the massive transfusion of patients with gastrointestinal or obstetric bleeding.

The investigators conducting the PROPPR clinical trial prospectively compared the 24 hour and 30 day all-cause mortality of severe trauma patients randomized to transfusion of red blood cells, plasma, and platelets in a 1:1:1 and a 2:1:1 ratio in a multicenter trial of trauma centers in the United States and Canada. The results of this study demonstrated no significant difference in either the 24 hour or 30 day all-cause mortality between the two study populations. The authors do make a statement that more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination at 24 hours. Additionally, there were no significant differences among 23 pre-specified complications, including multiple organ failure and adult respiratory distress syndrome, despite the 1:1:1 patients having received more plasma products over the first 24 hours of the study.

Slide 12:

The figure depicted on slide 12 is a schematic of the massive transfusion protocol at my institution. We currently utilize a RBC to plasma ratio of 2 to 1. Our protocol can be activated by an attending physician at our institution. The initial cooler contains 4 RBCs and 2 plasma. If crossmatch compatible RBCs are not available, emergency released O+ or O(-) (depending on the Rh status, age, and sex of the patient) will be issued. Type specific (if type known) or group AB plasma will be issued. It is very important for the blood bank to receive a properly labeled specimen for type and screening of these patients to avoid the continued need for universal donor, and thus, limited in inventory, group O RBCs and group AB plasma.

The second “massive pack” is issued 20 minutes later and consists of another cooler of 4 RBCs, 2 plasma, along with an apheresis platelet (issued separately, i.e., not in a cooler). After the first 3 coolers (roughly an hour after initiation of the MHTP), a dose of cryoprecipitate is issued. Additional doses of cryoprecipitate are issued every hour thereafter. Massive packs will continue to be prepared until the clinical team calls the blood bank to report that the protocol is no longer needed.

Slide 13:

Antifibrinolytics are increasingly becoming part of the massive transfusion protocol at many institutions. Tranexamic acid and amicar are lysine analogs that inhibit fibrinolysis by binding to plasminogen and preventing plasminogen from binding to a fibrin clot (where it may be activated to plasmin). These drugs also bind to plasmin and displace it from the fibrin clot.

The CRASH-2 trial was a prospective, multicenter, international randomized controlled trial of 20,211 adult trauma patients with or at risk of significant bleeding within 8 hours of injury who were assigned to either tranexamic acid (loading dose of 1g over 10 minutes then infusion of 1g over 8 hours) or placebo. The primary outcome was death in hospital within 4 weeks of injury. This large study showed that all-cause mortality was significantly reduced with tranexamic acid. The risk of death due to bleeding was also significantly reduced in the tranexamic acid group. There were no adverse events regarded as serious, unexpected, or suspected to be related to the study treatment.

Slide 14:

Lab testing may be incorporated into the massive transfusion protocol. Specimens should be sent early and often. Our institution recommends sending CBC, PT/PTT, and fibrinogen at the start of the protocol and every hour thereafter. The obstetric-specific massive transfusion protocol at Stanford recommends sending initial labs upon initiation of the protocol followed by repeat labs with each request for continued massive packages. Even “super-STAT” labs, such as those from the emergency hemostasis panel developed by the University of Washington (with a goal turn-around-time of 20 minutes), however, may not be helpful in the acute phase of the protocol. Additionally, some facilities have adopted the use of thromboelastography (TEG) and thromboelastometry (ROTEM) as part of their massive transfusion protocol; these tests are point-of-care devices that assess the coagulation process in close to real time. These devices, however, are not widely available and again, these results may not be helpful in the acute phase of a massive bleed. All of the above labs are most useful in the maintenance phase of a massive hemorrhage protocol.

Slide 15:

In developing massive transfusion protocols, a multidisciplinary approach is important. Discussions should include all shareholders invested in creating such protocols including, but not limited to: physicians, nursing, anesthesia, pharmacy, chemistry and hematology laboratories, as well as the blood bank.

Review of the massive transfusion protocol activations should ideally be presented at least annually to a facility’s transfusion committee for discussion. Such presentations may give rise to alterations in existing protocols or even the creation of discipline-specific massive transfusion protocols; for instance, some hospitals have obstetric-specific protocols with earlier transfusion of plasma and cryoprecipitate due to the physiologic changes that occur during a woman’s pregnancy and delivery. Regardless of the actual ratio of products of each institution’s massive transfusion protocol, continuous assessment should be performed and changes made as deemed necessary following transfusion committee discussion.

Slide 16:

There are many definitions of massive transfusion in the transfusion medicine literature. Massive bleeding occurs in many clinical settings such as trauma, gastrointestinal bleeding, cardiac surgery, and obstetric hemorrhage. There are numerous pathophysiologic changes that occur from receipt of massive transfusion. Protocols for massive transfusion have been shown to reduce mortality; however, the ideal ratio of products is still up for debate.

Slide 17: References

Slide 18: Disclosures

Slide 19: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on “Massive Transfusion.” My name is Kerry O’Brien.