Managing Massive Transfusions in diverse Patient Populations in a Non-Metropolitan Area

SHAUNA M.M. STURGILL, LAURIE GILLARD

LEARNING OBJECTIVES

1. Compare and contrast massive transfusion protocols for adults, obstetrical, and pediatric patients.
2. Discuss the complications of massive transfusions for each patient population.
3. List the pharmacological agents that can be useful when a massive hemorrhage is suspected.
4. Define critical access facility

ABSTRACT

Massive transfusion protocols have been developed to provide the best patient outcomes by administering the correct ratio of blood components and pharmacological agents available in today's market. Adults, obstetrical, and pediatric patients all have different needs during a massive hemorrhage. Patient outcomes, utilization of resources in a cost-effective manner, and education can all impact how this is accomplished. Through a literature review, this article outlines assesses the presence (or absence) of standard massive transfusion protocols for different patient populations in non-metropolitan areas where resources such as blood components can be difficult to obtain.

ABBREVIATIONS: AABB – organization formerly known as the American Association of Blood Banks), RBCs - packed red blood cells, APTT - activated partial thromboplastin time, FDA - Food and Drug Administration, FFP - fresh frozen plasma, TRALI - transfusion acquired acute lung injury, TACO - transfusion associated circulatory overload, TXA - Tranexamic acid, rVIIa - Recombinant factor VIIa, PCCs - Prothrombin Complex Concentrates, PPH - postpartum hemorrhage

INDEX TERMS: Massive transfusion; obstetrical, postpartum hemorrhage; pediatric hemorrhage

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***Shauna M.M. Sturgill, MLS(ASCP)^{CM}**, St Charles Medical Center, Bend, OR*

***Laurie Gillard, MS, MLS(ASCP)^{CM}SBB**, Rush University, Chicago, IL*

***Address for Correspondence: Laurie Gillard, MS, MLS(ASCP)^{CM}SBB**, Director of the Specialist in Blood Banking Certificate Program, Rush University, Chicago, IL 60612*

INTRODUCTION

Managing massive hemorrhaging in patients in a non-metropolitan area requires knowledge of current practices in massive transfusion, an understanding of what blood products and factor concentrates are available and their uses, and the different needs of each patient class. When managing a massively hemorrhaging patient, time is of the essence when activating an institution's massive transfusion protocol as many departments come together to manage the patient's care. Also, with institutions being challenged with soaring health care costs and resource utilization, it is imperative to determine the impact that the formation of massive transfusion protocols may have in the non-metropolitan area.

Products Used in Massive Transfusions

For the purpose of this paper, a critical access facility is defined as a non-metropolitan area that is greater than or equal to two hours away from a blood supplier. The current definition of a massive transfusion for an adult according to the AABB (formerly known as the American Association of Blood Banks) Technical Manual is "the receipt of more than 10 RBC units within 24 hours." The definition of what a massive hemorrhage entails depends on the patient type and will be defined in their respective section of this paper.

Blood components required for a massive transfusion include packed red blood cells (RBCs), plasma,

cryoprecipitate, and platelets. Pharmacological agents such as tranexamic acid (TXA), recombinant factor VIIa (rVIIa), and prothrombin complex concentrates (PCC) can aid in the management of bleeding during a massive transfusion. These pharmacological agents can be lifesaving when there is limited blood supply or when there may be a delay in replenishing the blood supply, which often occurs in a non-metropolitan area.

Red blood cells deliver oxygen to the brain and tissues of the human body. When there is a massive hemorrhage tissue oxygenation will be affected. When selecting red cell products they should be a compatible ABO blood type and for females of child bearing potential, Rh matched. Red blood cells are stored between 1 to 6 °C and require minimum preparation for transfusion. In emergent cases, such as a massive transfusion, patients should receive Group O red cells until a definitive blood type can be tested and recorded from a current specimen.[1]

Plasma contains many of the coagulation factors needed to maintain hemostasis and plays an important role in massive transfusion protocols by aiding in the reversal of coagulopathies. Fresh frozen plasm (FFP) is stored at 18 °C and thawed prior to use. Once thawed, plasma can be stored up to 5 days at 1- 6 °C if relabeled as 5-day thawed plasma. Plasma carries risks of TRALI (transfusion acquired acute lung injury), TACO (transfusion associated circulatory overload), infectious disease, and hemolytic transfusion reactions if ABO incompatible plasma is used for transfusion. When transfusing plasma, it should be compatible with the patient's red cells. Some institutions have begun using Group A plasma in trauma situations due to the difficulty in maintaining the universal donor Group AB.[2]

Cryoprecipitate primarily contains fibrinogen, Factor VIII, and von Willebrand factor, but the main use for cryoprecipitate in massive transfusions is fibrinogen replacement. Per the AABB Standards for Blood Banks and Transfusion Services, 30th edition, one unit of cryoprecipitate should contain a minimum of 150 mg of fibrinogen to be acceptable for transfusion. Fibrinogen is used in the primary and secondary stages in coagulation. Platelets require fibrinogen to function and for clot formation. Cryoprecipitate is stored at -18 °C for 1 year and once thawed it is stable for 4 to 6 hours at room temperature. Cryoprecipitate does not have any compatibility requirements for transfusion; therefore any ABO group is acceptable. Cryoprecipitate carries the risk of infectious disease transmission to patients.

Platelets are stored at 20-24 °C with constant agitation for 5 days before they expire. They are either collected as a single donor apheresis unit or derived from a whole blood donation. Approximately five whole blood derived platelets equate to one single donor apheresis platelet. Due to their short life span, platelets are harder to acquire and maintain adequate inventory, especially in remote areas. There is also a higher risk of bacterial contamination than other blood components due to their warmer storage temperature. In a patient with a massive hemorrhage, it is recommended that platelet counts be maintained above 50,000/mcL to ensure proper clot formation.

Whole blood has been used in massive transfusions of traumas but primarily in a military setting which is monitored by different regulatory agencies. It is difficult to obtain fresh whole blood for a massive transfusion since these types of events are usually not planned events. Whole blood, according to the AABB Standards, needs to be "ABO group-specific" for the recipient due to the anti-A and anti-B antibodies located in the plasma of the donor. Although some institutions will use Group O whole blood with low anti-A and anti-B titers, this does not seem practical in a massive transfusion setting due to staffing and time constraints to perform such testing on the units.

Tranexamic acid, or TXA, is an antifibrinolytic drug that should be in a massive transfusion protocol. When a massive hemorrhage is suspected, this should be one of the first drugs administered to the patient in addition to blood components. It aids in clot formation and has been shown to reduce the quantity of blood products a patient receives. It is also relatively inexpensive compared to rFVIIa and does not appear to have as many side effects. For a cost comparison, a single dose of TXA is approximately twenty-five dollars compared to a single dose of rFVIIa which is approximately five thousand dollars.[3]

rFVIIA is an expensive drug that has been used to stop bleeding in a hemorrhaging patient. It has been shown to cause more side effects such as thrombosis in the legs, heart, and lungs along with possible organ failure. Also,

it may be "less effective in patients with significant acidosis or hypothermia,"[4] which are common side effects of massive transfusions. Most providers have not been using this for stopping massive hemorrhages since the side effects cause additional problems the patient does not need.[4]

Prothrombin Complex Concentrates (PCCs), primarily four-factor PCCs, have been used off label in massive hemorrhage and rapid reversal of warfarin. There is only one four-factor PCC approved in the United States with most of their usage and research from Europe. The main risk of using a four-factor PCC is thrombosis.[4]

Complications of Massive Transfusions

When a massive transfusion protocol is initiated and the patient begins to receive blood products, there are potential complications that need to be monitored. Citrate toxicity from the anticoagulant in the blood products is one complication to be aware of. Citrate toxicity occurs when the anticoagulant citrate binds the patient's calcium during the transfusion and causes low serum calcium levels in the patient. This can lead to depressed cardiac function and neurological issues. Complications that arise from citrate toxicity usually do not need intervention; slowing the rate of transfusion or administering calcium can aid in reversing any complications the patient may be experiencing.

When large amounts of blood products are rapidly infused, hypothermia may occur. Hypothermia slows down the body's ability to maintain coagulation, affects platelet activation, and leads to cardiac complications.[5] The patient may also already be in a hypothermic state due to shock, blood loss from the trauma, and exposure to the elements. Blood products should be transfused through a Food and Drug Administration (FDA) approved blood warmer to help avoid additional hypothermia or initiating hypothermia through blood transfusion.

Adult Patients

In the adult trauma patient population, early plasma delivery improves patient outcomes. Current guidelines recommend that a 1:1 ratio of red cell products to plasma products be given to keep the patient hemodynamically stable. Some studies have shown that a 1:1:1 ratio of red cells, plasma, and platelets could lead to better outcomes as well.[6] In a non-metropolitan area, access to platelets are often limited to stock on hand to treat all patients and product replenishment does not happen quickly.

There are conflicting opinions on when it is optimal to add cryoprecipitate in a massive transfusion protocol. Some researchers or institutions leave it to the provider to decide and others have stated to transfuse cryoprecipitate when the fibrinogen level reaches 100 g/dL. This can also be dependent on if any anti-fibrolytic agents have been used in the treatment of the patient, such as TXA.

To aid in proper product management and delivery, certain laboratory values should be monitored during a massive transfusion. The patient's coagulation should be monitored with fibrinogen levels, a pro-time (PT), activated partial prothrombin time (APTT), and platelet count.[7] Thromboelastography (TEG) is not usually available in most non-metropolitan areas, but is a valuable coagulation monitoring assay if available. The patient's hemoglobin or hematocrit, potassium, ionized calcium and base excess are also important values to monitor since they can show some of the early signs of massive transfusion complications that can arise from citrate toxicity and potassium imbalance. It has been recommended that these laboratory values be monitored every 30 minutes and many can be tested using point of care devices, which minimizes additional blood loss.

Obstetrical Patients

Current guidelines recommend that the 1:1 use of red cells and plasma be used in postpartum hemorrhage (PPH), the same as with adult trauma patients. It is also recommended that with every six to eight units of red cells that one unit of apheresis platelets be transfused. PPH should also be monitored with laboratory tests that include fibrinogen, since that can provide a higher predictive value of excessive bleeding in obstetrical patients compared to the PT or APTT. It is important to activate a massive transfusion protocol in the early stages of a PPH. The earlier the laboratory values for coagulation are tested and evaluated, the sooner the correct product ratios can be obtained for a better patient outcome.[6]

When an obstetrical patient begins receiving blood components, it is important to assess their fibrinogen level early in a suspected PPH and provide cryoprecipitate, TXA, or both, if clinically indicated.

Fibrinogen is one of the first coagulation factors consumed by the body and is diluted when red blood cells are transfused. The normal range for fibrinogen in a woman at full-term pregnancy is higher for obstetrical patients than in the general adult population. Massive transfusion protocols for the general population are not administered until the fibrinogen level drops below 100 g/dL. In a full-term delivery, a fibrinogen level below 200 g/dL is a predictive value for a PPH.[6] A poor outcome or hysterectomy could result if the fibrinogen concentration continues to fall without being replaced. Some research has demonstrated that if TXA is provided to the patient at the onset of PPH, a reduced amount of blood products are required, diminishing the likelihood of a hysterectomy for the patient.[8]

It appears that there is still apprehension in administering TXA for PPH or activating an institutional massive transfusion protocol in obstetrical practice. When a survey was provided to faculty and in-training obstetricians regarding transfusion knowledge and PPH, there was a 93.8% response that more training is needed for transfusion medicine, especially in the administration of non-red cell products and their uses. This survey covered all topics including the use of TXA in PPH.[9]

Pediatric Patients

Massive transfusion in pediatric cases has not been well studied. The definition of a pediatric massive transfusion is when the child receives greater than or equal to 40 mL/kg of any blood component in a 24-hour period.[10] The largest concerns with the pediatric population in regard to massive transfusion are hypothermia and hyperkalemia since hypothermia has a negative effect on coagulation and hyperkalemia can induce cardiac arrest. This can be more prominent in the pediatric population due to their small size.[11]

Currently, there are no established guidelines addressing when to activate a pediatric massive transfusion protocol, leaving this decision up to physicians and institution policies and procedures. Almost all published studies have agreed that adult criteria should not be used to determine when to activate a massive transfusion in the pediatric population. One reason that adult criteria does not work for predicting massive transfusions in pediatrics is that vital signs and reference ranges vary with age and the pediatric population has many different age subsets during development.[12] With limited pediatric protocols, there are still unanswered questions in regard to the correct ratio of blood products, the effectiveness of massive transfusions for children, or what predictive values should be used in determining when to initiate a massive transfusion protocol.[13]

There is some research from combat zones, that has not been studied in civilian areas, of the use of TXA and the ratio of plasma to red cells products in the pediatric population. This study showed that pediatric patients who received a 1:1 ratio of plasma to red cells had a higher mortality rate than the pediatric patients who received slightly less plasma to a red cell ratio of 0.8:1. TXA in a combat setting seems to reduce mortality in the pediatric cases, but there needs to be additional controlled studies done in a civilian pediatric population before stating that anti-fibrinolytics are safe to use. One study stated that physicians should be cautious in the use of rFVIIa in the pediatric population.[14]

An issue with current guidelines for the pediatric population is with the use of saline or lactated ringers solution before the infusion of red cells. These crystalloid solutions appear to add to the dilution effect of coagulation factors and can cause the child to become hemodynamically unstable and may contribute to increased morbidity for the patient. It appears that crystalloid infusions for volume replacement could be contraindicated in pediatric massive transfusions and the adult population as well.[14]

When administered to this patient population, all fluids should be warmed to aid in the reduction of hypothermia. It has also been stated that rapid infusers should not be used for the pediatric population for massive transfusions and the rate of flow obtained should be just enough to keep the patient hemodynamically stable. The consensus is that there should be less emphasis on using the adult guidelines for a massive transfusion protocol in the pediatric population since they are not accurate for this population. Additional studies need to be performed to obtain accurate data on correct dosing of blood products, pharmacological agents, and their effectiveness on patient outcomes.[11]

CONCLUSION

Additional research is still needed for pediatric patients and massive transfusion protocols. This patient population has unique transfusion requirements making

it difficult to have a standard massive transfusion protocol for all patient populations. In a non-metropolitan area, strong consideration should be given to having TXA easily available to providers that provide obstetrical and trauma care. This has been shown to improve care for the patient, stabilize coagulopathies, and be cost effective by reducing the amount of blood products used. In addition to TXA, cryoprecipitate should be available at all non-metropolitan facilities providing obstetrical care.

A final piece to implementing a massive transfusion protocol in a non-metropolitan facility is education. Providers and laboratory staff need continuous education in regard to available blood products, their uses, and preparation time. Providers should also receive additional education from pharmacy professionals regarding pharmacological agents available and their uses in stopping a massively hemorrhaging patient. These recommendations can help improve patient care, aid in a successful implementation massive transfusion protocol, keep health care costs down, and manage resources wisely in the event of massive hemorrhage in a non-metropolitan area.

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