

Fresh Frozen Plasma

LTC Clayton D. Simon, MC, USA

MAJ(P) Jeremy Perkins, MC, USA

LTC Paul Barras, AN, USA

COL Brian Eastridge, MC, USA

COL Lorne H. Blackbourne, MC, USA

INTRODUCTION

For years, much has been said and written concerning the transfusion practices in the massively bleeding patient. It makes intuitive sense to transfuse whole blood in the massively bleeding patient since that is exactly what the patient is losing. However, since whole blood is not a product that is available for common hospital use, crystalloids and packed cells are commonly infused to treat the massively bleeding. Infusing a crystalloid solution (normal saline or lactated Ringer's solution) or stored packed red blood cells without clotting factors into a hemorrhaging patient will dilute the clotting factors and can actually make the patient more coagulopathic.¹⁻⁶ Clearly, the severely injured patient does not bleed crystalloid.

There have been a lot of recent discussions on the benefits of fresh frozen plasma (FFP) in combat wounded. This paper provides some basic information on FFP.

WHAT IS FRESH FROZEN PLASMA?

When a donor gives a unit of whole blood, the blood is separated into several components parts. The major components are packed red blood cells (pRBC), FFP, and sometimes platelets. The FFP can be further separated into cryoprecipitate and what is known as "cryo-poor plasma," a product rarely used for therapeutic means. Plasma is the liquid, noncellular portion of blood, and contains water, electrolytes, and proteins. The proteins in plasma include the major clotting factors and intrinsic anticoagulants. The plasma is separated from whole blood after donation and then frozen. To be

considered "fresh," the plasma must be placed into the freezer within 8 hours of collection and stored at minus 18°C or lower, otherwise it is just frozen plasma (another product rarely used for therapeutic means). FFP can be prepared either by separation from whole blood or collection via plasmapheresis.

Fresh frozen plasma contains the majority of all known coagulation factors, but essentially no cells (eg, red blood cells or white blood cells) nor platelets. In addition to the coagulation factors, FFP also contains approximately 500 mg of fibrinogen. Of note, the fibrinogen in 1 unit of FFP is approximately equal to the amount of fibrinogen found in 2 units of cryoprecipitate.⁷ These clotting factors and fibrinogen are critical for normal hemostasis.

COAGULOPATHY AND DAMAGE CONTROL SURGERY

Damage control surgery is the method of treating severely wounded patients in the combat zone. It applies the principles of an abbreviated operation to stop bleeding without completely restoring anatomy and returning the patient to the intensive care unit for resuscitation, warming, and correction of coagulopathy (inability to form clot) before returning to the operating room.⁸⁻¹⁰ The civilian data on damage control patients reveals a clear correlation between coagulopathy and mortality. Macleod et al demonstrated an increased mortality (19% mortality) if a trauma patient has a documented elevation in their prothrombin time (PT) versus those patients with a normal PT (5% mortality) on admission to the emergency department.¹¹ Furthermore, if a patient returns to the intensive care unit after the



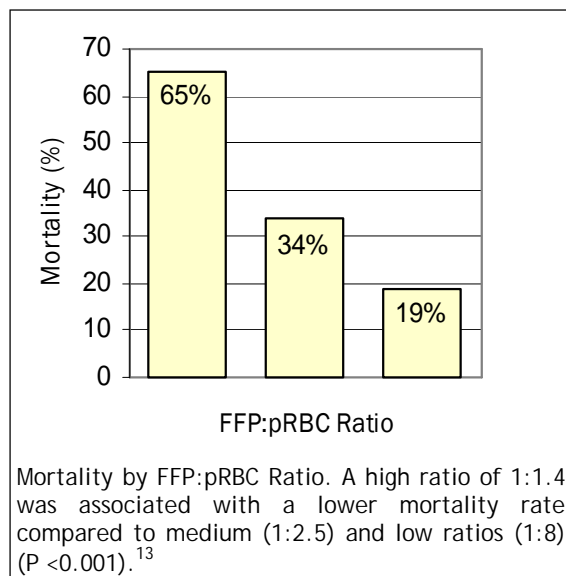
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abbreviated damage control operation and is coagulopathic, the probability of death is much higher and correlates with the degree of coagulopathy.¹²

COMBAT DATA

Combat wounded patients have severe soft tissue injuries and amputations not often seen in civilian trauma; and the coagulopathy seen in trauma patients may be even more of a consequence in these patients. Retrospective analysis from a combat support hospital has revealed a mortality benefit associated with infusing FFP to pRBCs in a 1:1.4 ratio (clinically, in the chaos of treating a hemorrhaging trauma patient this is transfused in a 1:1 ratio) in severely injured patients.¹³ In this study, mortality for each of the FFP:pRBCs ratios increased as more pRBCs were



transfused for fewer units of FFP. With an FFP:pRBC ratio of 1:8, the mortality was 65%. The mortality was 34% for the FFP:pRBC ratio of 1:2.5, but the high FFP:pRBC ratio of 1:1.4 resulted in a mortality of 19%.¹³ The data is presented in the Figure. From these retrospective data, it appears evident that the severely injured, coagulopathic patient needs not only oxygen carrying capacity and volume from packed red blood cells, but also clotting factors from FFP in a high ratio approaching a 1:1 ratio.

FFP STORAGE AND PREPARATION

When frozen FFP is maintained at -18°C , it is good for 12 months. Food and Drug Administration regulations require that FFP be stored at a temperature no higher

than -18°C , and according to the standards published by the American Association of Blood Banks, "Fresh Frozen Plasma shall be prepared from a whole blood or apheresis collection and frozen at less than or equal to -18°C ."¹⁴ Most commercially available small freezer units can easily maintain temperatures of -20°C , making FFP available for extended storage at all far forward medical facilities.

Thawing FFP is a simple process. It is the widely accepted practice to place the desired units in a warm water bath of 30°C to 37°C for 20 to 30 minutes with gentle agitation. Von Heymann, et al evaluated the effects of 2 commercially available thawing devices and running warm water (43°C) on the activity of clotting factors, inhibitors, and activation markers in fresh-frozen plasma. From 1 hour to 6 hours after thawing, no significant differences in the activity of the investigated coagulation markers dependent on the thawing procedure were found.¹⁵ If the thawed FFP is immediately transfused, it remains rich in clotting factors. This product can be rapidly infused intravenously through a warming device set at 37°C to 40°C . If the thawed FFP is not infused immediately it can be maintained at room temperature for up to 4 hours, or stored for up to 5 days at 1°C to 6°C .

THAWED PLASMA

If thawed FFP is not transfused within 24 hours, it is considered a distinct product termed "thawed plasma." While most clotting factors are stable in thawed plasma, some factors including V and VIII (termed *labile factors*) degrade over time and this degradation accelerates while plasma is stored in the liquid state. The advantage of having thawed plasma on hand is that it is immediately available for infusion to the severely injured patient. Many stateside blood banks have adopted this policy of maintaining thawed plasma for immediate release. In an effort to decrease request-to-infusion times, some larger trauma centers even maintain thawed plasma at 1°C to 6°C in the operating room.

UNIVERSAL FRESH FROZEN PLASMA DONOR

While it is common knowledge that O- is the universal donor for pRBCs, the same cannot be said for FFP. The A and B antigens of the blood are found on the red cells themselves. The type O individual is devoid of these proteins on the red cells. Plasma, on the other hand, contains the antibodies to the corresponding

absent protein. For example, a blood type A individual has Anti-B antibodies in his blood. Type O plasma has both Anti-A and Anti-B antibodies and is incompatible with about 55% of the population. However, an individual with type AB blood has neither Anti-A nor Anti-B antibodies. This makes the AB plasma ideal for universal use when the blood type of the patient is unknown. The Rh status is irrelevant because any plasma with Anti-D (the D protein is commonly referred to as Rh) is destroyed at the manufacturing stage. Considering the fact that only 4% of the population is blood type AB (and thus, the donor pool for the universal donor is very small) the best FFP to transfuse is blood type "compatible" based on the blood type determined in the blood bank and should replace the universal donor as soon as possible.

FUTURE

The future direction for combat damage control resuscitation will likely include synthetic hemoglobin as a replacement for pRBCs, especially in far forward environments. In the canine model this product is already available in the form of Oxyglobin® (Biopure Corporation, Cambridge, MA) and is actually used by veterinarians during canine trauma surgery today.¹⁶ This "synthetic blood product" consists of chemically stabilized hemoglobin in a balanced salt solution. When administered intravenously, this stabilized hemoglobin immediately circulates in the plasma and delivers oxygen to the body's tissues and organs. It is only a matter of time before this type of product is available for human use. Freeze-dried clotting factors or a combination of recombinant clotting factors like NovoSeven® (Novo Nordisk, Inc, Princeton, NJ), a recombinant factor VII, will possibly replace FFP (or act in synergy with FFP). Freeze dried or cryopreserved (frozen) platelets may someday replace our current platelets (platelets currently have a 5 day shelf life!). All of these components will need a long shelf life and preferably be heat stable to provide the full benefit of blood and blood product support for severely injured service members far forward in an austere combat environment.

CONCLUSIONS

Coagulopathy clearly correlates with mortality in severely injured damage control patients. Combat injured casualties represent a unique subset of these patients often with massive tissue injury. While

administering packed red blood cells replaces oxygen carrying capacity, it is deficient in coagulation factors. Whole blood administration accomplishes both red cell and plasma replacement, but is both labor and time intensive. Aggressively replacing the lost clotting factors approaching a 1:1 ratio of FFP to pRBCs should be a goal in all abbreviated damage control operations and intensive care unit resuscitation of all severely injured patients undergoing a massive blood transfusion (>10 units of pRBCs in 24 hours) in the combat zone. This is accomplished by assuring FFP is readily available and pushing FFP far forward to surgical facilities on the battlefield.

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AUTHORS

LTC Simon is Director of Blood Services, Brooke Army Medical Center, Fort Sam Houston, Texas.

MAJ(P) Perkins is Deputy Director, Military Casualty Research Division, and Chief, Department of Blood Research, Walter Reed Army Institute of Research, Bethesda, Maryland.

LTC Barras is Assistant Chief Nurse Anesthetist, Womack Army Medical Center, Fort Bragg, North Carolina.

COL Eastridge is Surgical Director, Surgical Intensive Care Unit, Brooke Army Medical Center, Fort Sam Houston, Texas.

COL Blackburne is Commander, Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas.

