Plasma components: An Update from COBM

In today's blood bank environment several plasma products are available for transfusion. In 2006, 77.2% of the plasma transfused in the USA was fresh frozen plasma (FFP).[1] This product is prepared from whole blood or apheresis donations and is frozen within 8 hours of collection.[2] Once thawed, plasma contains all clotting factors at physiological levels although there is considerable variability between donors in their level of individual clotting factors.[3] However, since anti-HLA antibodies are often implicated in causing transfusion related acute lung injury (TRALI),[4] and because multiparous females are often sensitized to HLA antigens,[5] many donor centers are diverting the plasma component of female donations to fractionation. To make up the shortfall in plasma supply, there are several other plasma products that can be prepared. Plasma frozen within 24 hours of phlebotomy (FP24) is an AABB/FDA approved plasma product, which as its name suggests, represents plasma that is frozen between 8-24 hours after collection. In 2006 it made up approximately 15% of the transfused plasma in the USA. Several studies have demonstrated that most clotting factor levels are well maintained in FP24 such that it is often used interchangeably with FFP.[6,7,8,9] Once thawed, both FFP and FP24 can be maintained in the liquid state for up to 24 hours at refrigerator temperatures. Previously both products would have been discarded after 24 hours, however recent studies have demonstrated that both FFP[10,11,12] and FP24[13,14] can be maintained as thawed plasma (TP) for up to 5 days in the refrigerator with minimal degradation of clotting factor levels. Although the AABB/FDA have only approved the use of TP prepared from FFP, in light of this evidence several transfusion services are routinely providing TP prepared from FP24. Note that none of these other plasma products have been directly compared to FFP in efficacy studies; however, given that they all demonstrate similar clotting factor levels to FFP, there is no *a priori* reason to suspect that they would be any less effective in reversing a significant coagulopathy or reducing bleeding. Thus, although "FFP" is commonly ordered, there are several other products that might be issued by the blood bank, so a more generic term of "plasma" should be adopted.

The indications for plasma transfusion include reversal of a significant coagulopathy in a bleeding patient or one who is about to undergo a surgical procedure; bleeding in the setting of multiple factor deficiencies; or, in the rare patient with a deficiency of a factor for which there is no viral-inactivated/recombinant concentrate available. Regardless of the setting, plasma use should always be guided by coagulation tests.[15] Laboratory parameters, in conjunction with a clinical assessment of the patient, that would support the use of plasma include a prolongation of the PT to greater than 1.5 times the middle of the reference range, INR $\geq$1.6, or an aPTT greater than 1.5 times the top of the normal range.[16,17] Thromboelastography can also be used to guide therapy.[18] A mild to moderate coagulopathy, defined as an INR < 1.5, does not appear to be associated with excessive bleeding[19,20] In addition, the mean INR of plasma is 1.1 while the range is 0.9 – 1.3 thus plasma transfusion has limited to no effect in circumstances where a mild or moderate coagulopathy is present.[21] The availability of FP24 may help reduce the increased use of plasma in non-bleeding patients with elevated INR by waiting to see if microvascular

bleeding occurs and then transfusing the plasma. Many patient with INR of < 2.5 may be able to clot without plasma transfusion. Since plasma can be stored for days after thawing, having it available and returning plasma back to the blood bank if not used reduce inappropriate use and conserves this resource.

In emergent situations, plasma may be used to reverse the effect of warfarin prior to surgery or during active bleeding episodes. However, if time allows, oral or parenteral (IV) vitamin K will reverse an elevated INR in 6-12 hours without exposing patients to the risks associated with human blood components. The hemostatic effect of the appropriate dose (see below) of plasma generally lasts for approximately 8 hours[22], thus if plasma is being used for emergent reversal of warfarin, it should be given close to the start of any invasive surgical procedure and in conjunction with vitamin K administration. On the other hand once plasma is transfused it, like all blood products, remains almost entirely in the intravascular space. This needs to be borne in mind because rapid infusion rates, intended to facilitate the administration of the entire dose of plasma before the start of the surgery, could lead to circulatory (volume) overload. Plasma should not be transfused prophylactically in patients undergoing cardiopulmonary bypass in the absence of diffuse microvascular bleeding[23], nor should it be used as a volume expander or as a source of nutrition.

The literature on fixed RBC:plasma ratios in the resuscitation of trauma patients is controversial and based mainly on retrospective and observational studies with significant methodological and/or statistical limitations.[24,25] No recommendation at this time can be made for a specific ratio of plasma to red cells in massive transfusion despite many trauma center's adoption of such ratios.[26] No data exists for aggressive plasma transfusion outside of the massive trauma setting. When plasma is indicated, it should be administered in a dose of at least10-15 mL/kg.[27,28] Although a dose of 5-8 mL/kg has previously been recommended for warfarin reversal[29], more recent guidelines suggest 10-15 mL/kg should be used.[30] It is important to remember that hypothermia and acidosis should be corrected prior to plasma administration.

References

1. US Department of Health and Human Services. The 2007 national blood collection and utilization survey. Washington, DC: DHHS, 2009.
2 . Brecher ME. Technical Manual. 16th ed. Bethesda, MD: AABB, 2008.
3. Holland LL, Foster TM, Marlar RA, Brooks JP. Fresh frozen plasma is ineffective for correcting minimally elevated international normalized ratios. Transfusion 2005;45: 1234-5.
4. Triulzi DJ. Transfusion-related acute lung injury: an update. Hematology Am Soc Hematol Educ Program 2006: 497-501.
5. Kakaiya RM, Triulzi DJ, Wright DJ, Steele WR, Kleinman SH, Busch MP, Norris PJ, Hillyer CD, Gottschall JL, Rios JA, Carey P, Glynn SA. Prevalence of HLA antibodies in remotely transfused or alloexposed volunteer blood donors. Transfusion 2010;50: 1328-34.

6. Kakaiya RM, Morse EE, Panek S. Labile coagulation factors in thawed fresh frozen plasma prepared by two methods. Vox Sang 1984;46: 44-6.
7. O'Neill EM, Rowley J, Hansson-Wicher M, McCarter S, Ragno G, Valeri CR. Effect of 24-hour whole-blood storage on plasma clotting factors. Transfusion 1999;39: 488-91.
8. Smith JF, Ness PM, Moroff G, Luban NL. Retention of coagulation factors in plasma frozen after extended holding at 1-6 degrees C. Vox Sang 2000;78: 28-30.
9. Cardigan R, Lawrie AS, Mackie IJ, Williamson LM. The quality of fresh-frozen plasma produced from whole blood stored at 4 degrees C overnight. Transfusion 2005;45: 1342-8.
10. Downes KA, Wilson E, Yomtovian R, Sarode R. Serial measurement of clotting factors in thawed plasma stored for 5 days. Transfusion 2001;41: 570.
11. Sidhu RS, Le T, Brimhall B, Thompson H. Study of coagulation factor activities in apheresed thawed fresh frozen plasma at 1-6 degrees C for five days. J Clin Apher 2006;**21**: 224-6.
12. Scott EA, Puca KE, Pietz BC, Duchateau BK, Friedman KD. Comparison and stability of ADAMTS13 activity in therapeutic plasma products. Transfusion 2007;47: 120-5.
13. Yazer MH, Cortese-Hassett A, Triulzi DJ. Coagulation factor levels in plasma frozen within 24 hours of phlebotomy over 5 days of storage at 1 to 6 degrees C. Transfusion 2008;48: 2525-30.
14. Scott E, Puca K, Heraly J, Gottschall J, Friedman K. Evaluation and comparison of coagulation factor activity in fresh-frozen plasma and 24-hour plasma at thaw and after 120 hours of 1 to 6 degrees C storage. Transfusion 2009.
15. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM: Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br J Haematol 2004; 126: 11-28
16. Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A,Fung M, Hamilton M, Hess JR, Luban N, Perkins JG, Sachais BS, Shander A, Silverman T, Snyder E, Tormey E, Waters J, Djulbegovic B. Evidence-based practice guidelines for plasma transfusion. Transfusion 2010;50:1227-1239.
17. Coagulation management in trauma-related massive bleeding. Recommendations of the working group on Perioperative Coagulation of the ÖGARI. 2010
18. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, RIddez L, Schultz A, Stahel PF, Vincent JL, Spahn DR. Managemnt of bleeding following major trauma: an updated European guideline. Critical Care 2010;14:R52-R81.
19. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. Br J Haematol 2004;126: 139-52.
20 Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion 2005;45: 1413-25
21. Holland LL, Foster TM, Marlar RA, Brooks JP. Fresh frozen plasma is ineffective for correcting minimally elevated international normalized ratios. Transfusion 2005;45: 1234-5.

22. Hambleton J, Wages D, Radu-Radulescu L, Adams M, MacKenzie M, Shafer S, Lee M, Smyers J, Wiesehahn G, Corash L: Pharmacokinetic study of FFP photochemically treated with amotosalen (S-59) and UV light compared to FFP in healthy volunteers anticoagulated with warfarin. Transfusion. 2002;42: 1302-7
23. Cross-sectional guidelines for therapy with blood components and plasma derivatives (edited by the Bundesärztekammer) Transfus Med Hemother 2009;36:419-36
24. Phan HH, Wisner DH. Should we increase the ratio of plasma/platelets to red blood cells in massive transfusion: what is the evidence? Vox Sang 2010;98: 395-402
25. Murad MH, Stubbs JR, Gandhi MJ, Wang AT, Paul A, Erwin PJ, Montori VM, Roback JD. The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. Transfusion 2010;50:1370-83.
26. Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A,Fung M, Hamilton M, Hess JR, Luban N, Perkins JG, Sachais BS, Shander A, Silverman T, Snyder E, Tormey E, Waters J, Djulbegovic B. Evidence-based practice guidelines for plasma transfusion. Transfusion 2010;50:1227-1239.
27. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, RIddez L, Schultz A, Stahel PF, Vincent JL, Spahn DR. Managemnt of bleeding following major trauma: an updated European guideline. Critical Care 2010;14:R52-R81.
28 Chowdhury P, Br J Haematol 2004;125:69-73
29. Questions and answers about transfusion practices. 3rd Ed. American Society of Anesthesiologists Committee on Transfusion Medicine. Pg 14. 1997
30. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM: Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br J Haematol 2004; 126: 11-28