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Fresh Frozen Plasma for Transfusion: A Review

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INTRODUCTION

Plasma transfusions have increased steadily over the last 15 years – 2.3, 3.9 and 4.1 million units were transfused in 1991, 2001 and 2004, respectively.[1] US use is disproportionately high compared to other countries. Wallis *et al.* reported that rates of plasma distribution in the US exceed those of some developed countries, *e.g.* >3-fold higher rates in the US compared to France and 2-fold higher than in the UK.[2]

Fresh frozen plasma (FFP) is separated from whole blood by centrifugation, or by apheresis and frozen within 8 hours of collection. It contains all of the plasma coagulation factors, including labile factors V and VIII.

FP24. Plasma frozen within 24 hours of phlebotomy (FP24) increasingly is substituted for FFP, in part to allow production of plasma for transfusion from male-only donors to reduce the risk of transfusion-related acute lung injury (TRALI) associated with white blood cell antibodies from alloimmunized multiparous female donors. FP24 contains slightly lower levels of factors V and VIII, but their replacement with plasma is rarely indicated. Most consider FFP and FP24 therapeutically equivalent.[3]

When stored at ≤-18ºC, both FFP and FP24 have a shelf life of 12 months. FFP produced and stored at ≤-65ºC may be stored up to 7 years. Collection volumes vary, dependent on the method of collection.

INDICATIONS & CONTRAINDICATIONS

Accepted indications for FFP are shown in Table I. FFP is not effective in patients with coagulation factor inhibitors and is contraindicated for volume expansion, nutritional support, or to enhance wound healing.[4]

There is growing concern about unnecessary plasma transfusion for abnormal coagulation tests without bleeding.[2,5] As awareness of the adverse reactions to plasma transfusion grows, especially TRALI and transfusion associated circulatory overload (TACO),[7] there are increasing calls for the judicious use of plasma.

TABLE I: Indications for FFP Transfusion (*Circular of Information*, 2002)[6]

- Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors (*e.g.*, liver disease)
- During massive transfusion
- Bleeding patients on warfarin or who need to undergo an invasive procedure before vitamin K can reverse the warfarin
- Plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)
- Management of patients with congenital or acquired coagulation factor deficiencies for which specific coagulation concentrates are unavailable
- Rare plasma protein deficiencies, *e.g.,* C-1 esterase inhibitor

FFP IN RESPONSE TO PROLONGED PT/INR

Plasma often is transfused to nonbleeding patients to correct abnormal coagulation tests – especially the prothrombin time or international normalized ratio (PT/INR) – with the assumption that this will limit the risk of clinical bleeding. Multiple studies have questioned the clinical validity of this assumption, however.[8]

In a systematic review of studies conducted between 1966 and 2004, Segal and Dzik[6] evaluated patients undergoing invasive procedures with a normal or abnormal PT/INR. They included 24 observational studies and one clinical trial. None demonstrated a statistically significant association of increased bleeding risk with the abnormal lab result. They concluded that, while the evidence is of poor quality, there is little evidence that modest prolongation of PT/INR predicts bleeding after an invasive procedure.

Abdel-Wahab *et al*. explored the assumption that FFP transfusion can correct a prolonged PT/INR and challenged the assumption that abnormal coagulation tests are predictive of bleeding.[9] In an audit of all FFP transfusions at the Massachusetts General Hospital between September 2, 2004 and September 30, 2005, they analyzed transfusions to patients with an INR of 1.1 - 1.85, who had a follow-up INR within 8 hours of transfusion. Of 1,091 FFP transfusion episodes, 121 patients (324 units) qualified for the study. FFP transfusion resulted in the normalization of PT/INR in only 0.8% of patients and decreased the PT/INR halfway toward normal in only 15% of patients. The median decrease in PT/INR result was 0.20 seconds (INR 0.07). There was no association of increasing plasma dose with greater correction. Pretransfusion PT/INR, partial thromboplastin time, platelet count, and creatinine had no correlation with estimated RBC loss.

Abdel-Wahab *et al.* concluded that transfusion of FFP for mild abnormalities of coagulation values normalizes PT/INR in a tiny minority of patients, failing to correct the PT in 99% of patients. This is consistent with other studies demonstrating no significant correlation between the pretransfusion PT/INR value and the estimated risk of blood loss.

In a review of these and several more studies, Triulzi concluded that available data do not support the efficacy of plasma for bleeding or prophylaxis for invasive procedures in patients with a mild coagulopathy – defined as an INR of less than 2.0.[8] Acknowledging that there were many weaknesses in the designs of the existing studies, Triulzi also described the prospective, randomized Study of Hemostasis in Invasive Procedures (SHIP) trial from the Transfusion Medicine/Hemostasis Clinical Trials Network. SHIP was to involve 16 sites and 1,300 participants undergoing invasive hepatic procedures with a pre-procedure INR of 1.3 to 1.9, randomly assigned to plasma, or no treatment.[8] Unfortunately, this trial foundered for lack of enrollment – so the current evidence base must be used to provide guidance on appropriate plasma transfusion.

Plasma therapy for mild to moderate prolongation of the PT/INR is widespread, but appears ineffective and unnecessary. In the absence of a definitive trial, growing concern for adverse reactions to plasma therapy warrants reassessment of this practice.

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