



[haematologica reports]  
2006;2(10):71-74

## Use of Fresh Frozen Plasma and Plasma Proteins in Newborn Infants

M.J. MANCO-JOHNSON<sup>1</sup>  
N.L.A. GOLDENBERG<sup>1,2</sup>

<sup>1</sup>Departments of Pediatrics<sup>1</sup> and  
<sup>2</sup>Medicine University of Colorado at  
Denver and the Health Sciences  
Center and The Children's Hospital,  
Denver, CO, USA

A B S T R A C T

Clinically significant hemorrhage, especially intracranial hemorrhage, is a major cause of morbidity and mortality in extremely preterm infants and is a rare event in otherwise healthy term infants. Infusions of FFP in newborn infants is effective in reducing blood loss associated with extracorporeal membrane oxygenation or cardiopulmonary bypass and to treat active bleeding due to disseminated intravascular coagulation, liver failure or vitamin K deficiency. However, routine use of fresh frozen plasma (FFP) in sick preterm infants for volume expansion, to treat coagulopathy in the absence of bleeding, or for partial exchange transfusion does not decrease mortality or morbidity.

*Correspondence:*  
Marilyn J. Manco-Johnson, MD  
Professor of Pediatrics  
Address: Mountain States  
Regional Hemophilia & Thrombo-  
sis Center  
Phone: 011-303-724-0365  
Fax: 011-303-724-0947

**U**tization of blood resources remains high in neonatal intensive care units. Sick newborn infants, especially preterm infants, are likely to receive blood products including fresh frozen plasma for many reasons, including: acute bleeding, coagulopathy, exchange transfusion, priming the circuit for extracorporeal membrane oxygenators (ECMO) or cardiopulmonary bypass (CPB), blood volume expansion and sepsis. This paper will examine evidence underlying use of fresh frozen plasma (FFP) or plasma protein components in each of these settings.

### **Acute Bleeding**

Clinically significant hemorrhage is a major cause of morbidity and mortality in extremely preterm infants and a rare event in otherwise healthy term infants.

### **Intracranial Hemorrhage (ICH) in sick preterm infants**

Hemorrhage in sick preterm infants is frequently intracranial (ICH) and occurs with a highest frequency during the first seventy-two hours of life.<sup>1</sup> Early studies determined that infants less than thirty-two weeks gestation manifested laboratory evidence of hypocoagulability with low fibrinogen, thrombocytopenia and prolonged bleeding time prior to the onset of ICH.<sup>2</sup> The finding of decreased antithrombin, in itself a prothrombotic risk factor, in these infants suggested that hypocoagulability in sick extremely preterm infants resulted from a consumptive coagulopathy.<sup>2</sup> Based on these

findings, a small randomized clinical trial (RCT) to prevent ICH in high risk infants using transfusions of fresh frozen plasma (FFP), 10 mL per kg, versus no routine replacement at birth and again at 24 hours, was performed in the early 1980's by Beverley et al. and showed encouraging results (3). Subsequently, the Northern Neonatal Nursing Initiative Trial (NNNIT) included infants less than 32 weeks gestation in a large RCT (N=776) administering FFP, 30 mL/kg, versus no routine replacement, during the first 24 hours of life, and were unable to demonstrate an improvement in survival or neurodevelopmental outcome.<sup>4</sup> Finally, a recent Cochrane meta-analysis of five clinical trials including these two and three additional trials concluded that routine infusion of FFP in ill preterm infants failed to show benefit with respect to overall mortality, ICH incidence or long-term outcomes.<sup>5</sup>

The rate of ICH in sick preterm infants decreased and the mean gestational age of infants with severe ICH decreased in association with improvements in neonatal supportive care.<sup>6</sup> A recombinant preparation of the activated procoagulant protein, factor VII (rFVIIa), has been used successfully in several case reports to treat ICH in preterm infants.<sup>7</sup> A RCT using rFVIIa as treatment of neonatal ICH is in preparation (presented to the International Society of Thrombosis and Haemostasis, Subcommittee on Perinatal and Pediatric Haemostasis, by P. Mathews, University of New Mexico).

### ***ICH and other severe bleeding manifestations in term infants***

Symptomatic ICH in term infants is rare and is most often associated with complications in labor and delivery.<sup>8</sup> Severe symptomatic intracranial, gastrointestinal, skin or abdominal bleeding following an uneventful delivery raises the possibility of early hemorrhagic disease of the newborn or a severe genetic bleeding disorder. After excluding thrombocytopenia, screening coagulation studies should be performed to rule out vitamin K deficiency, and hemophilia A or B caused by deficiencies of factors VIII or IX, respectively. Less common bleeding disorders associated with neonatal intracranial and other hemorrhages include afibrinogenemia as well as severe deficiencies of factors XIII, X, VII and V. If none of the more common coagulopathies is evident, term infants with ICH in the absence of obvious trauma should be further evaluated for these rare disorders as well as for hyperfibrinolysis (including severe deficiencies of the plasminogen activator inhibitor (PAI-1) or  $\alpha_2$ -antiplasmin) or severe platelet function abnormalities. Vitamin K should be administered to all infants at birth.

While there are no RCTs of term infants with ICH, it would appear reasonable to administer FFP, 10-20 mL/kg, to replace a potential coagulation factor deficiency while awaiting results of coagulation factor assays. Once the diagnosis of a genetic bleeding disorder has been determined, it is appropriate to use specific factor replacements as available (Factors VIII, IX, VII, XIII, fibrinogen, von Willebrand factor), cryoprecipitate (fibrinogen, factor XIII) or FFP (factors II, V, X, XI, PAI-1 and  $\alpha_2$ -antiplasmin). Routine prophylactic replacement of clotting factors is generally not required in newborn infants with these coagulopathies but should be used for bleeding, surgery, or invasive procedures.

Rarely, ICH may result from post-infarction hemorrhage. The anatomic distribution in the area of the middle cerebral artery suggests neonatal ischemic arterial stroke in affected infants.

### ***ECMO and CPB***

ECMO is used in extremely preterm infants with severe respiratory distress who fail mechanical ventilation. The use of standardized protocols to administer FFP, packed red blood cells (PRBC) and platelet concentrates to infants on ECMO has been shown to reduce hemorrhage safely with minimal adverse impact on blood resources.<sup>9,10</sup> Similar to ECMO, CPB used during cardiac surgery often requires FFP and other blood products to prime the bypass circuit and to control bleeding. A large RCT of infants undergoing CPB (N=96) showed that FFP and PRBC were superior to whole blood for pump priming regarding outcomes

including hospital stay and cumulative fluid balance.<sup>11</sup> Three retrospective reviews of FFP and PRBC for CPB in children have shown low rates of bleeding, acceptable overall blood component use and favorable clinical outcomes.<sup>12-14</sup>

### ***Liver Disease***

Neonatal liver failure, caused by severe intrauterine infection or primary liver disease, is marked by severe coagulopathy and clinical bleeding. The coagulopathy of liver disease is complex and includes decreased coagulation protein synthesis, thrombocytopenia, platelet dysfunction, hyperfibrinolysis and diminished clearance of fibrin degradation products. Although objective evidence from RCTs is lacking, the mainstay of therapy for bleeding associated with neonatal liver failure is the infusion of FFP in doses of 10-20 mL/kg. The magnitude and duration of effect of FFP depends on the volume of distribution (limited to the plasma volume for factor VIII, XIII and fibrinogen, and to twice the plasma volume for the vitamin K-dependent proteins II, VII, IX, and X) and half-life (ranging from six hours for factor VII to ten days for factor XIII) of deficient coagulation proteins. There is no evidence that FFP is of benefit in the absence of bleeding (15). However, prophylactic use of FFP in the setting of coagulopathy of liver disease is appropriate prior to liver biopsy or other invasive procedures.

### ***Sepsis and disseminated intravascular coagulation (DIC)***

Hemorrhage is a frequent complication of sepsis in neonates, particularly among preterm infants. Thrombocytopenia is the most frequent coagulopathy in infants with sepsis and bleeding, followed by DIC with low fibrinogen and a prolonged prothrombin time. The mainstay of therapy for DIC in the neonate is treatment of the underlying cause with appropriate antibiotics and support of perfusion and oxygenation. Clinical bleeding is treated with infusions of FFP to replace consumed procoagulant factors reflected in a prolonged prothrombin time and cryoprecipitate to replace consumed or dysfunctional fibrinogen. There is no evidence that treatment of asymptomatic coagulopathy is beneficial. A small RCT (N=33) assigning neonates with DIC randomly to treatment with exchange transfusion, FFP and platelet concentrates or no transfusion support in addition to aggressive supportive care showed no difference in mortality or resolution of DIC in either of the two treatment groups.<sup>16</sup> A more recent study of plasma exchange for the treatment of DIC in children with meningococemia showed no significant advantage.<sup>17</sup>

With regard to targeted coagulation interventions for DIC, an open-label German treatment trial of 10

newborn infants with DIC and acquired antithrombin (AT) deficiency or persistent coagulopathy on heparin therapy was conducted administering AT concentrate at 40 U/kg/day and unfractionated heparin at 50 to 500 U/kg/day. In this trial, eight of ten infants survived and seven of eight survivors had improvement in coagulopathy within two days of initiation of therapy. The investigators reported a mean increase in plasma AT activity of only 8%, suggesting that neonates in DIC may require higher dosing for efficacy due to increased consumption of AT. Whether among neonates, older children or adults, no definitive evidence existed that a coagulation treatment of sepsis and DIC altered outcome until the report in 2001 of a 19% relative reduction in mortality associated with infusions of recombinant activated protein C (drotrecogin alpha, Xigris, Eli Lilly, Indianapolis, IN) in adults.<sup>18</sup> Unfortunately, ICH was subsequently observed as a major toxicity in 5.9% of children treated with this drug on an international, open-label pediatric protocol.<sup>19</sup> Thus, activated protein C cannot be routinely recommended in sick newborn infants with sepsis and DIC at this time.

### **Exchange transfusion**

Complete exchange transfusion for the management of severe unconjugated hyperbilirubinemia of the neonate is most often required in the setting of alloimmune Rh or ABO hemolytic anemia. Early studies determined that clinical outcomes in neonates were equivalent for the use of blood reconstituted from FFP and PRBC as compared with fresh whole blood for complete exchange transfusion.<sup>19</sup> Partial exchange transfusion is generally limited to newborn infants with hyperviscosity secondary to polycythemia. FFP was not found to be superior to normal saline in three RCTs of neonatal hyperviscosity, whether measured by short-term reduction in hematocrit or long-term neurologic outcome.<sup>20-22</sup> Current understanding that chronic intrauterine hypoxia is pivotal in the pathophysiology of neurologic damage in neonatal hyperviscosity syndrome explains why postnatal red cell reduction using partial exchange transfusion improves organ perfusion but does not prevent abnormal neurologic outcomes.<sup>23,24</sup>

### **Purpura fulminans**

Purpura fulminans is uncommon in the newborn infant. The neonatal syndrome of early onset DIC, purpura fulminans (particularly originating from pressure points) and large vessel thrombosis is nevertheless important to recognize and is caused by homozygous or compound heterozygous mutations in the protein C or protein S genes. After a blood sample is obtained for confirmatory plasma assays of protein C activity and

free and total protein S antigen, affected neonates should be treated with 10 mL/kg of FFP every eight hours until the diagnosis is confirmed or excluded. A highly-purified, viral-inactivated, plasma-derived protein C concentrate (Ceprotin, Baxter HeathCare, Marlburg, Germany) is licensed in Europe and currently undergoing Food and Drug Administration (FDA) review in the United States. Protein C concentrate is highly effective in prophylaxis and treatment of DIC secondary to severe genetic protein C deficiency (< 20 IU/dL).

Purpura fulminans secondary to bacterial sepsis also occurs in newborn infants and is explained by acquired deficiency of components of the protein C system. Treatment is similar to that for DIC and sepsis, although use of protein C concentrate or activated protein C may be useful to limit tissue infarction. Indeed pediatric studies in older children suggest favorable outcomes as compared to historical controls in a single institutional study.<sup>26</sup>

### **Neonatal thrombosis**

Standard antithrombotic therapy for the newborn infant consists of anticoagulation using unfractionated or low molecular heparin or thrombolysis using tissue plasminogen activator or urokinase. Effective anticoagulation is sometimes limited in the newborn infant by low plasma levels of AT and thrombolysis is sometimes limited by low plasma concentrations of plasminogen, caused both by physiologic development and rapid consumption. Both AT and plasminogen may be replaced in neonates with thrombosis using FFP at 10 mL/kg once daily. Because of rapid clearance, it may be difficult to increase AT to clinically relevant levels with FFP. Although not studied in the context of a clinical trial, highly purified, viral-inactivated, human plasma-derived AT concentrate may be used in doses of 50-100U/kg every 24 to 48 hours to replace this protein and increase heparin sensitivity in infants who fail to achieve the target therapeutic anti-Xa activity using usual doses of heparins.

### **Conclusion**

Optimal use of FFP and plasma protein components in the newborn infant requires a careful consideration of indications, risks and benefits. In general, routine infusion of FFP into asymptomatic infants to treat coagulopathy is without measurable benefit. In contrast, FFP is effective to treat hemorrhage in infants with clotting factor deficiency caused by vitamin K deficiency, genetic clotting factor deficiency, consumptive coagulopathy, liver failure, ECMO or CPB. Blood reconstituted from FFP and PRBC is effective for complete exchange transfusion but FFP is not superior to saline in partial exchange transfusion.

## References

1. McDonald MM, Koops BL, Johnson ML, Guggenheim MA, Rumack CM, Mitchell SA, and Hathaway WE. Timing and antecedents of intracranial hemorrhage in the newborn. *Pediatrics* 1984;74:32-6.
2. McDonald MM, Johnson ML, Rumack CM, Koops BL, Guggenheim MA, Babb C, Hathaway WE. Role of coagulopathy in newborn intracranial hemorrhage. *Pediatrics* 1984;74:26-31.
3. Beverley DW, Pitts-Tucker TJ, Congdon PJ, Arthur RJ, and Tate G. Prevention of intraventricular haemorrhage by fresh frozen plasma. *Arch Dis Child* 1985;60:710-3.
4. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. Northern Neonatal Nursing Initiative Trial Group. *Lancet* 1996; 348:229-32.
5. Osborn DA and Evans N. Early volume expansion for prevention of morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev* 2004; 2:CD002055.
6. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. *Pediatrics* 2001;107;1-D01: 10.1542/peds.107.1.e1
7. Mathew P. The use of rFVIIa in non-hemophilia bleeding conditions in paediatrics. A systematic review. *Thromb Haemost* 2004;92:738-46.
8. Rosenberg EM, Chambers LA, Gunter JM and Good JA. A program to limit donor exposures to neonates undergoing extracorporeal membrane oxygenation. *Pediatrics* 1994;94:341-6.
9. McCoy-Pardinton D, Judd WJ, Knalf P, et al. Blood use during extracorporeal membrane oxygenation. *Transfusion* 1990;30:307-9.
10. Mou SS, Giroir BP, Molitor-Kirsch EA, Leonard SR, Nikaidoh H, Nizzi F, Town DA, Roy LC, Scott W, and Stromberg D. Fresh whole blood versus reconstituted blood for pump priming in heart surgery in infants. *N Engl J Med* 2004; 351:1635-1644.
11. Petaja J, Lundstrom U, Leijala M, Peltola K, and Siimes MA. Bleeding and use of blood products after heart operations in infants. *J Thorac Cardiovasc Surg* 1995; 109:524-529.
12. Nicolas F, Daniel JP, Bruniaux J, Serraf A, Lacour-Gayet F, and Planche C. Conventional cardiopulmonary bypass in neonates. A physiological approach—10 years of experience at Marie-Lanlongue Hospital. *Perfusion* 1994; 9:41-48.
13. Chambers LA, Cohen DM, and Davis JT. Transfusion patterns in pediatric open heart surgery. *Transfusion* 1996; 36:150-154.
15. O'Shaunessy DF, Atterbury C, Maggs PB, et al. (for the British Committee for Standards in Haematology Blood Transfusion Task Force.) Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004;126:11-28.
16. Gross SJ, Filston HC, Anderson JC. Controlled study of treatment for disseminated intravascular coagulation in the neonate. *J Pediatr* 1982;100:445-8.
17. Churchwell KB, McManus ML, Kent P, et al. Intensive blood and plasma exchange for the treatment of coagulopathy in meningococemia. *J Clin Apheresis* 1995;10:171-4.
18. Bernard GR, Vincent JL, Laterre PF, et al. Recombinant human protein C worldwide evaluation in severe sepsis (PROWESS) study group. *N Engl J Med* 2001;344:699-709.
19. Goldstein B, Nadel S, Peters M, et al. ENHANCE: results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. *Pediatr Crit Care Med* 2006;7:200-11.
19. Barnard DR, Chapman RG, Simmons MA, Hathaway WE. Blood for use in exchange transfusion in the newborn. *Transfusion* 1980;20:401-8.
20. Supapannachart S, Siripoonya P, Boonwattanasoontorn W, and Kanjanavanit A. Neonatal polycythemia: effects of partial exchange transfusion using fresh frozen plasma, Haemaccel and normal saline. *J Med Assoc Thai* 1999;82(Suppl 1):S82-6.
21. Roithmaier A, Arlettaz R, Bauer K, et al. Randomized controlled trial of Ringer solution versus serum for partial exchange transfusion in neonatal polycythaemia. *Eur J Pediatr* 1995;154:53-6.
22. Deorari AK, Paul VK, Shreshta L, and Singh M. Symptomatic neonatal polycythemia: comparison of partial exchange transfusion with saline versus plasma. *Indian Pediatr* 1995;32:1167-71.
23. Rothenberg T. Partial plasma exchange transfusion in polycythemic neonates. *Arch Dis Child* 2002;86:60-62.
24. Rosenkrantz TS. Polycythemia and hyperviscosity in the newborn. *Semin Thromb Hemost* 2003;29:515-27.
26. Rivard GE, David M, Farrell C, Schwarz HP. Treatment of purpura fulminans in meningococemia with protein C concentrate. *J Pediatr* 1995;126:646-52.