

PLASMA AND ALBUMIN TRANSFUSIONS: INDICATIONS AND CONTROVERSIES

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Albumin plays an important role in health and disease. Albumin is a major contributor to colloid oncotic pressure (COP), binds endogenous and exogenous molecules, mediates coagulation, and helps to maintain normal microvascular permeability. The clinical consequences of hypoalbuminemia reflect these varied functions. Significant hypoalbuminemia contributes to increased morbidity and mortality. Albumin can be administered via the transfusion of plasma products, or via the infusion of human serum albumin (HSA).

ALBUMIN

Albumin, a 69,000 protein, is synthesized in the liver. Physiologic hepatic synthesis occurs at approximately 30% of capacity, replacing about 4% of total body albumin daily. During times of increased need, hepatic synthesis increases dramatically. In health, synthetic rate is influenced predominantly by COP. When COP decreases, albumin synthesis increases. (Indeed, correction of hypoalbuminemia by synthetic colloid infusion can significantly depress albumin synthesis.) Inflammation decreases albumin synthesis by as much as 90%. Inflammatory cytokines shunt amino acids to increase synthesis of acute phase proteins important to the inflammatory process, and away from albumin synthesis.

Albumin is distributed between the intravascular (40%) and extravascular (60%) compartments, with a half-life of approximately 8 days. There is constant slow flux between these compartments. In cases of intravascular albumin loss, albumin moves from the extravascular to the intravascular compartment to maintain COP. Since serum albumin concentration measures only the intravascular portion, it may not be an accurate approximation of whole body albumin in diseased patients.

Albumin serves many diverse functions. The clinical consequences of hypoalbuminemia reflect the functions of the molecule. While mild hypoalbuminemia is generally of little consequence, moderate or severe deficiency can have life-threatening effects. Of major importance is the role of albumin in the maintenance of COP. Albumin is responsible for 50% of total plasma protein concentration and 80% of plasma COP. In critically ill patients, this relationship is less predictable. Albumin also appears to play a role in maintaining microvascular integrity. Although the mechanism is unclear, it is likely that albumin occupies water channels between endothelial cells to narrow the channels and repel macromolecules. Severe hypoalbuminemia results in extravascular fluid accumulation. Assuming normal vascular integrity, this generally does not occur until serum albumin decreases below 1.5 g/dl. When vascular integrity is compromised (eg, vasculitis), or in the face of intravenous fluid therapy, milder hypoalbuminemia can result in extravascation. Fluid accumulation is usually manifested as peripheral edema (distal limbs, ventrum, dependent areas), organ edema and/or cavity effusion. Pulmonary edema is less common and, in humans, is directly correlated with decreased survival. Edema can compromise wound healing, and gastrointestinal edema may lead to anorexia, decreased nutritional absorption, ileus, and enteral feeding intolerance, as well as exacerbation of hypoalbuminemia through GI loss.

Albumin binds a host of endogenous and exogenous substances, including bilirubin, calcium, edotoxin, and certain drugs (digoxin, furosemide, warfarin, several antibiotics). Hypoalbuminemia results in increased concentrations of protein-bound drugs in the unbound form, leading to either adverse effects or rapid metabolism and decreased efficacy. Albumin also binds and scavenges free oxygen radicals, and can bind iron, inhibiting lipid peroxidation. Hypoalbuminemia reduces these protective effects.

Albumin plays a role in modulating coagulation, by binding arachidonic acid and thus inhibiting the synthesis of thromboxane A_2 , and by augmenting the activity of antithrombin (AT). Significant hypoalbuminemia can cause or contribute to hyperaggregability in the predisposed patient.

Hypoalbuminemia is a common complication of multiple disease processes, and is associated with a worsened prognosis for recovery. Synthetic colloids, such as hydroxyethylstarch, can improve COP, but they cannot provide the multiple other vital functions of albumin. In human septic patients, a serum albumin < 2.0 g/dl has been correlated with increased mortality, even when COP is maintained via synthetic colloid infusion. Albumin administration decreases morbidity and, at least theoretically, may increase survival.

PLASMA TRANSFUSION

Plasma products

Centrifugation of whole blood separates the heavier red blood cells from plasma. Fresh frozen plasma (FFP) is separated from whole blood and frozen within 6 hours of collection. It contains equivalent amounts of all hemostatic proteins (coagulation factors, antithrombin, macroglobulin, etc), albumin and globulin as the plasma from which it was processed. FFP should be transfused within 1 year of collection. Frozen plasma (FP) is separated from whole blood and frozen more than 6 hours after collection. The term FP also describes FFP that has been stored for longer than 1 year. FP retains albumin, globulin, and activity of vitamin-K dependent factors (II, VII, IX, and X), but has lost activity of the more labile factors. It can be stored for up to 5 years. Cryoprecipitate (CP) is prepared from FFP to precipitate the heavier, cold-insoluble proteins. The resulting CP contains fVII, vWF, fibrinogen, and fibronectin with an average factor yield of 50%, in 10% of the original plasma volume. This concentration enables rapid administration of therapeutic factor levels. All plasma products should be stored at temperatures at or below -20°C.

Indications and Administration

Coagulopathies

Plasma components are indicated in disorders of secondary hemostasis, to control active hemorrhage, or as prophylaxis prior to surgery or other invasive procedures. The use of components prevents red cell transfusion, eliminating sensitization and reducing the volume of transfusion. Fresh frozen plasma (FFP) is most commonly used in veterinary practice. Because it contains hemostatic factors equivalent to the plasma from which it was obtained, it is indicated for the treatment and prevention of bleeding associated with almost all acquired and hereditary disorders of secondary hemostasis. An exception is heparin-induced bleeding, because the hemorrhagic diathesis is caused by factor inhibition, not deficiency; moreover, the antithrombin in FFP may enhance heparin effects. FP is adequate for deficiencies of factors II, VII, IX, and/or X. For the management of coagulopathies, FFP or FP is generally administered at a dose of 10-20 ml/kg over approximately 4 hours. The dose of plasma can be repeated as needed up to every 8-12 hours.

CP is indicated for the management of patients with vWD, fVIII deficiency (Hemophilia A), hypofibrinogenemia and dysfibrinogenemia. For vWD and fVII deficiency, CP is transfused at 1 unit per 10 kg body weight, over 20-30 minutes, and repeated every 4-12 hours as needed. If CP is not available, FFP may suffice, but is suboptimal. There is substantial evidence for a beneficial role of CP in the treatment of dilutional coagulopathy. The primary problem of disturbed fibrinogen/fibrin polymerization can be reversed by the administration of fibrinogen.¹ FFP is not effective for this indication due to its volume-expanding effect and low fibrinogen concentration. The administration of fibrinogen to human patients with massive bleeding or prolonged surgery has been shown to correct coagulation parameters, halt bleeding, and decrease transfusion requirements. There are, as of yet, no clear guidelines regarding a critical threshold for fibrinogen. Most transfusion algorithms do not treat fibrinogen levels unless <100-150 mg/dl, but one study showed concentrations < 200 mg/dl to be highly predictive for hemorrhage. The clinical utility of CP for dilutional coagulopathy in animals remains to be determined but, based on experimental animal and clinical human data, it is likely that it would be beneficial. Indications would include documented hypofibrinogenemia, decreased clot strength (determined via thromboelastography), and/or unrelenting hemorrhage following significant bleeding and fluid resuscitation (particularly if hetastarch was included in the resuscitative protocol). A CP dosage of 50-70 ml/10 kg (containing approx 500 mg/dl fibrinogen) was effective in controlling bleeding in 3 dogs with hypocoagulable DIC and postoperative hemorrhage.²

Hypoalbuminemia

FFP and FP can be used to supply albumin in patients with clinical signs associated with hypoalbuminemia, to reverse or ameliorate the consequences of such. Plasma contains 0.025g of albumin/ml. The dose of plasma required to increase albumin by 0.5 g/dl (5 g/l) is approximately 20-30 ml/kg/day, assuming no extraordinary loss or metabolism. To adequately replete albumin in a severely hypoproteinemic dog, large volumes of plasma are required. This is frequently cost prohibitive, especially in larger dogs. Synthetic colloid solutions are more efficacious, and more economical, as a means to increase COP. Colloids, however, cannot fulfill the multiple other functions of plasma. It is generally recommended to administer sufficient plasma to raise serum albumin to 2.0-2.5 g/dl, and to provide synthetic colloid in addition to maintain a COP of 15-20 mmHg. The volume of plasma to be transfused can be calculated from the above formula. This, however, serves only as a guideline; additional transfusion should be given as needed to achieve the target albumin concentration, based on serial measurement. The rate of infusion is based on the urgency of need and the volume tolerance of the patient; guidelines are as described for coagulopathies. Continuous infusion over 12-24 hours is not uncommon.

Other indications

FFP has been recommended in patients with severe pancreatitis. The rationale includes not only repletion of albumin, but the provision of α 2-macroglobulins and antiproteases. In spite of a correlation between albumin concentration and survival in human patients, a therapeutic benefit of albumin is not supported in the literature. FFP has also been recommended for use in puppies with parvoviral enteritis (to provide antibodies and immunoglobulins). Concrete evidence of a beneficial effect, however, is lacking.

General administration principles

Since plasma is a natural blood product, general principles of blood typing, cross-matching, and blood banking apply. Similarly, transfusion carries the usual risks of immunologic and nonimmunologic transfusion reactions.

Plasma products should be thawed gently to avoid protein denaturation that occurs with rapid warming or exposure to temperatures exceeding 39°C. This is best achieved in a commercial thawer. Where this technology is not available, the plasma should first be left to approach room temperature before placing it in a warm water bath. The temperature of the bath should be gradually increased to room temperature or slightly above. A blood filter is essential for all blood product transfusions to remove clots and cellular debris. An in-line blood filter (170-260 μ m pores) and drip chamber is incorporated into standard transfusion administration sets. A pediatric microaggregate filter with 40 μ m pore size (Hemo-Nate, Gesco International; San Antonio, USA) is useful for administering small volumes of blood to cats and small dogs via syringe.

Transfusion is initiated at 1-2 ml/kg/hr. If this is well-tolerated, the rate is increased up to 10-15 ml/kg/hr in the dog, and 2.5-4.0 ml/kg/hr in the cat. In the hypovolemic patient, this rate can usually be significantly increased. In the patient at risk for volume overload (cardiac disease, oliguria/anuria), administration rate should not exceed 2-4 ml/kg/hr in the dog and 1-2 ml/kg/hr in the cat. If transfusion is planned to exceed 4-6 hours, the plasma should be divided into aliquots, and that amount not to be used within 4-6 hours refrigerated until use. Synthetic colloid infusion should be halted during plasma transfusion to decrease the risk of volume overload.

HUMAN SERUM ALBUMIN

Human serum albumin (HSA) is manufactured from pooled human plasma that is ultrafiltrated and heat sterilized. It has a prolonged shelf-life without refrigeration. Hyperoncotic 25% HSA contains 0.25g albumin/ml (10 times that of plasma) and has a COP of 200 mmHg. (The COP of normal canine plasma is 20 mmHg, and that of 6% hetastarch 30-45 mmHg.) Because of this increased albumin concentration, it would appear an ideal solution for the management of patients with severe hypoalbuminemia, and there are reports indicating positive outcomes. However, the use of HSA remains controversial. Moreover, there

is a real risk of both immediate and delayed hypersensitivity reactions in animals associated with the use of a foreign antigen.

Human clinical trials show conflicting effects of HSA on outcome. Some of this can likely be explained by differing albumin preparations (4% vs 20% vs 25%) as well as by differing patient subpopulations. A 2004 trial compared the effects of resuscitation with 4% HSA versus saline, and found no difference in overall mortality in hypovolemic patients. Other trials have demonstrated a positive impact of 25% HSA in hypoalbuminemic critically ill patients with respect to organ function.

Despite increasing interest and use of HSA in critically ill veterinary patients, little data exists regarding indications and efficacy. Studies in critically ill dogs with a variety of underlying diseases (sepsis, pancreatitis, peritonitis, trauma) have shown that 25% HSA is effective in increasing albumin and protein concentrations, as well as COP. These studies have been retrospective in nature and included broad populations of patients such that statistically meaningful conclusions regarding survival impact cannot be drawn.

In healthy dogs, the administration of HSA results in detectable antihuman albumin antibodies within a week of infusion, which peak at 2-3 weeks. Immediate reactions have ranged from urticaria, facial swelling and/or vomiting to severe anaphylactic reactions, shock, and death. In one study of 9 healthy dogs administered HSA, one dog had a severe anaphylactic reaction, and 2 dogs developed urticaria and edema 6-7 days post-infusion.³ In another study of 6 dogs, 1 dog showed an immediate reaction, characterized by vomiting and facial swelling, while all dogs displayed delayed reactions, including lethargy, lameness, peripheral edema, renal failure, coagulopathy, and death.⁴ The incidence of hypersensitivity reactions is suggested to be less than in healthy dogs. Mathews et al reported facial edema in 2 of 66 patients, with no other adverse effects.⁵ Trow et al reported the use of HSA in 73 ill dogs; 23% has some form of complication (mostly minor) that might have been related to the infusion or the underlying illness, 4% had severe delayed complications.⁶ It remains unclear whether the higher incidence of adverse effects in healthy dogs is related to the infusion of albumin to euvoletic animals with a normal albumin, or to differences in dose and protocol. The majority of adverse events in healthy and diseased animals have responded to diphenhydramine and supportive care.

Administration

A reasonable goal for HSA administration in dogs is to increase serum albumin to 2.0-2.5 g/dl and COP to 15-20 mmHg. The dose is calculated by the following equation: albumin deficit (g) = 10 x (serum albumin goal – patient's serum albumin) x body weight (kg) x 0.3. (1ml 25% HSA supplies 0.25 g albumin.) The total dose should not exceed 1.25 g/kg. HAS is infused intravenously via a peripheral or central vein, alone or together with crystalloid fluids, over 4-72 hours. The more rapid infusion rate is reserved for the treatment of hypotension; slower rates have been associated with a more sustained increase in serum albumin. It has been suggested that aseptic dilution of HSA to a 10% solution with 0.9% NaCl, and administration over an extended period (12-hr) via a blood transfusion filter may decrease the prevalence and severity of reactions.

Recommendations

Albumin support is an important goal in all critical patients, particularly those with septic peritonitis, severe sepsis or undergoing surgery. The use of HSA should not be considered a replacement for plasma, but rather an adjunct to such therapy; FFP contains proteins, coagulation factors, and antiproteases that are not provided in concentrated albumin. Given the difficulty in providing sufficient plasma to correct hypoalbuminemia, the administration of HSA to critically ill, hypoalbuminemic patients may be of benefit. However, real risks of adverse reactions exist. When deciding if HSA is an appropriate therapeutic option, all risks should be considered and the owners educated in this regard.

REFERENCES

1. Mittermayr M, Streif W, Haas T et al: Hemostatic changes after crystalloid or colloid administration during major orthopedic surgery: the role of fibrinogen administration, *Anesth Analg* 105:905, 2007.
2. Vilar P, Ball R, Westendorf N et al: Hemostatic effects of cryoprecipitate in dogs with disseminated intravascular coagulation (abstract), *J Vet Intern Med* 23:692, 2009.
3. Cohn LA, Kerl ME, Lenox CE et al: Response of healthy dogs to infusions of human serum albumin, *Am J Vet Res* 68:657, 2007.
4. Francis AH, Martin LG, Haldorson GJ et al: Adverse reactions suggestive of type III hypersensitivity in six healthy dogs given human albumin, *J Am Vet Med Assoc* 230:873, 2007.
5. Mathews KA, Barry M: The use of 25% human serum albumin: outcome and efficacy in raising serum albumin and systemic blood pressure in critically ill dogs and cats, *J Vet Emerg Crit Care* 15:110, 2005.
6. Trow AV, Rozanski EA, de Laforcade AM et al: Evaluation of use of human albumin in critically ill dogs: 73 cases (2003-2006), *J Am Vet Med Assoc* 4:607, 2008.

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