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THE USE OF COLLOIDS IN CLINICAL PRACTICE

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A colloid fluid contains large molecular weight particles that are relatively impermeable to the semi-permeable membrane of the healthy vasculature. The number of particles in the colloid solution promote the retention of sodium and water around the core of the particle within the vascular space. Depending on the colloid oncotic pressure of the solution (COP), some colloid solutions can also draw fluid into the intravascular space from other fluid compartments in the body. Colloid fluids can be categorized as either natural or synthetic. Natural colloids include whole blood with plasma proteins, plasma, and concentrated albumin solutions.

Synthetic colloids include dextran-70, oxypolygelatin, hydroxyethyl starch and pentastarch. Colloid solutions are useful during the treatment of conditions associated with hypovolemic and septic shock, vasculitis, hypoproteinemia, and third-spacing of fluids such as pleural and peritoneal effusions and peripheral edema.

Indications for Colloids

Approximately 75 – 80% of an isotonic crystalloid fluid infused will leave the intravascular space within 1 hour of infusion. Infusion of a colloid fluid along with a crystalloid fluid will help retain the fluid within the vascular space for a longer period of time and have a sustained effect on intravascular volume expansion. For this reason, colloid infusions are often administered in combination with a crystalloid fluid during hypovolemic shock. Fluid also is retained within the intravascular space as a result of the net effect of the difference between oncotic and hydrostatic pressures within the intravascular and interstitial fluid compartments. An important factor in fluid retention is also the pore size of the vasculature. Any condition that is associated with sepsis, vasculitis, or systemic inflammatory response syndrome can predispose
the leakage of intravascular fluid into the interstitium. Additionally, conditions that are associated with hypoalbuminemia (albumin < 2.0 g/dL) can result in decreased intravascular COP to such an extent that capillary hydrostatic pressures predominate in favoring the efflux of intravascular fluid into the interstitium. Under normal circumstances, lymphatic drainage picks up excessive interstitial fluid and transports it back into the vasculature. In situations associated with increased intravascular hydrostatic pressure or decreased oncotic pressure, or with increased capillary pore size, lymphatic drainage can become overwhelmed and lead to interstitial edema.

SYNTHETIC COLLOIDS

Hydroxyethyl Starch Solutions

Hydroxyethyl starch (Hetastarch, Hespan, others) solutions contain a synthetic polymer of amylopectin, a highly-branched starch molecule in 0.9% saline or Lactated Ringers solution. The branched nature of the polymer produces a fluid that contains molecules of various sizes that range from 10,000 to 1 million Daltons. The weight-average of the solution is 69,000 – 71,000 Daltons, a molecule that is very similar in size to naturally occurring serum albumin. Approximately one-third of hetastarch remains in circulation after 3 days, and can be detected in serum for up to 17 weeks in humans. Smaller particles (< 50,000 Daltons) are degraded by serum amylase and are excreted by the kidneys. Larger molecules are metabolized by the reticuloendothelial system. In dogs, the half-life is shorter, at 7 – 9 days. Approximately 30% is degraded and eliminated within 24 hours. In dogs and cats, published recommended doses of hetastarch are 20 – 30 ml/kg/day due to the potential risks of coagulopathy as the amylopectin polymer binds with von Willebrand’s factor. In practice, however, this recommended dose can be exceeded when hydroxyethyl starch solutions are being used to improve blood pressure. The colloid infusion can be administered in 5 – 10 ml/kg incremental doses when attempting to
improve hypotension, and then continued as a constant rate infusion when using it to contribute to colloid oncotic pressure. In animals with low oncotic pressure, or hypoalbuminemia, supplemental colloid support should be continued until the source of albumin loss and clinical signs attributable to hypoalbuminemia (i.e. chemosis, pulmonary edema, peripheral edema) have resolved.

Pentastarch is also known as low-molecular-weight hetastarch. Pentastarch also contains polymers of amylopectin, with a more homogenous and average molecular weight of 30,000 Daltons. Pentastarch provides a rapid increase in blood volume within 1 hour of administration. Because of the smaller size of the majority of pentastarch particles, the elimination half-life is more rapid than hetastarch. Approximately 90% of pentastarch is cleared from circulation within 24 hours of administration, and the rest is gone after 3 days.

The amylopectin in both hydroxyethyl starch and pentastarch solutions is degraded by serum amylase, and as such, can result a mild increase in serum amylase concentration. By no means should this be interpreted as a cause and effect of hetastarch causing pancreatitis, as serum amylase concentration is a very insensitive clinical marker for this disease. Hydroxyethyl starch has been shown to bind with von Willebrand’s factor, and can raise the ACT and APTT slightly, although this is likely of little clinical significance unless administered to a patient with von Willebrand’s factor deficiency. When administered too rapidly, hydroxyethyl starch can cause histamine release in cats, and has been known to cause vomiting. Because of this effect, it is generally recommended to avoid rapid boluses of the solutions over less than 15 minutes time in this species.

Dextran 40 and Dextran 70
Dextran-containing solutions have also been used for decades to provide colloidal support, so deserve some mention here, although are not widely used in practice at this time. Dextran solutions are essentially polymers of glucose produced by a bacterium (Leuconostoc mesenteroides). Dextran-40 contains glucose polymers with an average molecular weight of 40,000 Daltons, and Dextran-70 contain glucose polymers with an average molecular weight of 70,000 Daltons. The half-life of the above solutions are approximately 30 minutes and 7-9 hours, respectively. Dextrans are excreted by the kidneys. Half-lives can be greatly prolonged in animals with renal insufficiency and decreased glomerular clearance. In addition, low-volume or hypotensive states can decrease or prolong renal clearance and cause precipitation of the polymer in the renal tubules. This can potentially lead to renal failure. For this reason, the use of dextran-containing fluids should be used with caution in hypovolemic, hypotensive, dehydrated patients, and those with renal dysfunction.\(^1\)

The administration of dextran-containing fluids is not innocuous. Humans and some small animals contain naturally occurring antibodies against the dextran molecule. These are thought to develop from exposure in dextran-containing foodstuffs. Rapid infusion of Dextrans, particularly Dextran-40, have been associated with anaphylactic reactions. For this reason, the use of Dextran-40 has largely fallen out of favor in both humans and veterinary patients. Dextran-70 can coat platelets and decrease aggregability, and can prolong bleeding times. This may be beneficial in hypercoagulable states such as that observed with hyperadrenocorticism or disseminated intravascular coagulation, but would largely be contraindicated in animals with thrombocytopenia or thrombocytopenia.

Oxypolygelatin
Gelatin solutions were initially developed for use in mass casualty situations, and are widely available in Europe. Gelatin solutions contain modified and urea cross-linked gelatin from bovine collagen origin. The average molecular weight of the particles in solution are approximately 30,000 – 35,000 Daltons. Because of the large number and small size of the particles in solution, oxypolygelatin acts as a potent colloid and draws a volume of fluid from the interstitial space into the vasculature equal to the amount administered. Oxypolygelatin has a relatively short half-life of 2 hours, but can be found in circulation for approximately 7 days after administration. Like other synthetic colloids, oxypolygelatin is excreted by the kidneys, and should be used with caution in animals with renal insufficiency or failure. The risk of anaphylaxis is low, but can occur. Although oxypolygelatin has not been shown to affect platelets or protein clotting factors, dilutional coagulopathies can occur after administration of large volumes.

**Concentrated Human Albumin**

Concentrated human and canine specific albumin solutions are now available for use in veterinary patients. During states of health, albumin contributes approximately 50% to the serum total protein and 80% to the serum colloid oncotic pressure. The majority of albumin within the body is located in the interstitial compartment, with a smaller amount located intravascularly. This becomes important in disease states associated with hypoalbuminemia. In such instances, the intravascular pool becomes replenished by the interstitial pool and hepatic synthesis until this supply becomes depleted. Albumin synthesis by the liver is stimulated by osmoreceptors in the hepatic sinusoids sensing a decrease in COP. In the presence of synthetic colloids, the osmoreceptors sense an artifactually increased to normal COP at the hepatic sinusoid, albumin production may be curtailed. Once significant hypoalbuminemia ([albumin] <
2.0 g/dL) develops, the intravascular hydrostatic pressure can exceed intravascular colloid oncotic pressure, and lead to efflux of fluid from the intravascular space into the interstitium and overwhelm the lymphatic drainage system and lead to interstitial edema.

In addition to contributing the majority of the colloid oncotic pressure within the body, albumin also has important functions as a mediator of coagulation, drug- and hormone carrier, scavenger of oxygen-derived free-radical species, and mediator of healing. In both human and animal patients with clinically significant hypoalbuminemia, morbidity and mortality is increased unless albumin stores are replenished. Plasma solutions contain small amounts of albumin, but are an inefficient and costly means of replenishing serum and interstitial albumin concentrations. To raise the serum albumin by 0.5 g/dL in a hypoalbuminemic animal, approximately 20 ml/kg of plasma must be administered. This dose increases if ongoing albumin losses are present.

Most recently, concentrated human albumin solutions have been used for a number of reasons, including treatment of hypoalbuminemia and decreased colloid oncotic pressure, and as a potent colloid in the treatment of hypotension. Both immediate and delayed rare hypersensitivity reactions have occurred in critically ill dogs, and include fever, vomiting, angioneurotic edema, delayed vasculitis and polyarthopathies. A recent prospective study documented a high rate of development of anti-albumin antibodies and complication when concentrated human albumin was infused into healthy, normoalbuminemic dogs. A limitation of this study was that all experimental dogs were normoalbuminemic; and received a very large dose (50 grams) of human albumin within one hour, rather than the recommended slower rate and smaller dose over 4 – 8 hours. The authors acknowledged that immunocompetence in normoalbuminemic dogs differed from critically ill animals, and may put the normoalbuminemic
animals at a particular risk of developing anti-human albumin antibodies and reactions to albumin infusion. In a later study, the researchers documented that all dogs, both experimental and clinical cases, that received human albumin developed anti-albumin antibodies within days to weeks after infusion. Early reactions occurred during albumin infusion, while delayed reactions occurred approximately 6 - 14 days later. Two healthy dogs that received concentrated human albumin developed vasculitis post-administration, and then died. Clients must be aware of the potential risks of complications; however, two studies have documented marked benefit and improved survival in animals that were poorly responsive to other more conventional therapies in the intensive care units. Because of the inherent risks associated with the administration of concentrated human albumin to dogs, its infusion should be restricted to animals with acute severe hypoalbuminemia whose clinical signs and conditions are not sufficiently treated with blood products and artificial colloids alone.

**Potential Complications Associated with Various Colloid Fluids**

Colloid fluids are a great resource that as practitioners, we can treat states of hypoalbuminemia and low oncotic pressure. However, the use of colloids can sometimes contribute to complications, as well. The use of a colloid will, in general, retain the fluid portion of any crystalloid fluid infused within the intravascular space for a longer period of time than if the crystalloid fluid was infused alone, without the colloid. Without a colloid, approximately 80% of a crystalloid fluid infused will leave the intravascular space within 1 hour of administration. With concurrent administration of a colloid, the crystalloid fluid will be retained within the vascular space for a longer period of time. This can potentially increase the capillary hydrostatic pressure and lead to interstitial, including pulmonary, edema. To avoid this potential complication, the crystalloid fluid volume should be decreased by 25 – 50% when a colloid is
infused concurrently. That is, only 50 – 75% of the calculated crystalloid fluid volume should
be administered to avoid the potential for interstitial edema. Both clinically and experimentally,
an increase in intravascular lung water during resuscitation from hemorrhagic shock can
decreased serum COP and decreased oxygen delivery. Refractometric readings of COP can be
artifactually decreased by the dilutional effects of hydroxyethyl starch or dextrans.

Hydroxyethyl starch can decrease Von Willebrand’s factor and Factor VII activities by
can be decreased to 40% of normal. Monitoring of the intrinsic clotting cascade, that is, the
activated clotting time (ACT) and activated partial thromboplastin time (APTT) may be elevated
from normal reference values in animals that have received hydroxyethyl starch. Platelet plug
formation may also be delayed in dogs after administration of various hydroxyethyl starch
solutions. This likely is not clinically significant and does not cause clinical bleeding until the
infusion exceeds the manufacturer’s recommended dose of no more than 20 – 30 ml/kg/day, or if
an animal has a hereditary coagulation disorder such as a Factor VII deficiency or von
Willebrand’s disease. Dextran 70 can promote neutrophil demargination and decrease
neutrophil counts in animals. Low-molecular weight dextrans have been associated with renal
tubular obstruction in animals with renal insufficiency. Dextrans can coat red blood cells and
platelets, and interfere with tests of coagulation and red-cell cross-match procedures. Dextran-
40 has been associated with an increased risk of anaphylaxis, and should be avoided, whenever
possible, as better options are available today for our veterinary patients.