Perioperative fluid therapy

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Oxygen Delivery During Anesthesia and the Rationale for Perioperative Fluid Therapy

General anesthesia of the surgical patient should provide reversible amnesia, analgesia, unconsciousness, muscle relaxation, and immobility. During the anesthetic period, every effort should be made to ensure homeostasis of the patient to minimize anesthetic complications and ensure a smooth and uneventful recovery. Many anesthetic drugs that provide these desirable qualities, however, adversely influence the hemodynamic status of the patient.[1-3] A principal consideration during anesthesia is to maintain microcirculatory organ perfusion and oxygen delivery to tissues to maintain cellular energy production. Perioperative fluid therapy is important to help maintain intravascular volume, optimize **cardiac output (CO)**, and ensure that **blood oxygen content (Ca_{O_2})** is adequate by ensuring an adequate concentration of **hemoglobin (Hb)**. **Oxygen delivery (D_{O_2})** is determined by Ca_{O_2} and CO:

$$D_{O_2} = Ca_{O_2} \times CO$$

Blood oxygen content is affected by **blood oxygen saturation (Sa_{O_2})**, Hb concentration, and the **partial pressure of oxygen in arterial blood (Pa_{O_2})**:

$$Ca_{O_2} = [(Sa_{O_2} \times Hb \times 1.34) + (Pa_{O_2} \times CO \times 0.003)]$$

The relationship between arterial **blood pressure (BP)**, CO, and **systemic vascular resistance (SVR)** is:

$$BP = CO \times SVR$$

Cardiac output is determined by **stroke volume (SV)** and **heart rate (HR)**:

$$CO = SV \times HR$$

Cardiac output is not routinely measured during anesthesia, and BP is an insensitive indicator of CO because of concurrent changes in SVR.

Stroke volume is influenced by preload, afterload, and myocardial contractility. Increases in preload, up to a point, increase cardiac output according to the Frank-Starling Law. Myocardial contractility is the inherent ability of the individual myocardial cells to contract and generate force. Increases in cardiac contractility, therefore, increase ejection fraction and SV. Anesthetic agents have various dose-dependent effects on the cardiovascular system, often with negative effects on preload and myocardial contractility.[4] Decreased SV and CO can result in hypotension if a compensatory increase in SVR does not develop, as is common during general anesthesia.[3] Substantial intraoperative arterial hypotension requiring immediate correction can be defined in a small animal patient as systolic blood pressure < 90 mm Hg or **mean arterial blood pressure (MAP)** < 60 mm Hg. When MAP decreases to < 60 mm Hg, there may be impaired perfusion of the brain and kidneys and loss of their ability to autoregulate blood flow.[5,6] Impaired renal blood flow can result in renal ischemia with subsequent acute tubular necrosis and acute renal failure.[7]

Anesthetic agents have other negative influences on fluid dynamics and cardiovascular function, including vasodilation and inhibition of the response to hypovolemia by the sympathetic nervous system.[8,9] This results in relative blood volume deficits in the surgical patient. Reduced tissue perfusion results in anaerobic metabolism and lactic acidosis.[10] Perioperative fluid therapy, therefore, is important to offset the negative effects of anesthetic agents on D_{O_2} to tissues and to stabilize the patient's hemodynamic variables. In a clinical setting, this is important because hypotension was the most common anesthetic complication (with prevalence of 7% in dogs and 8.5% in cats) in animals that underwent elective or nonelective procedures in 1 study.[11] A fluid administration rate of 10 to 15 mL/kg/h (4.5 to 6.8 mL/lb/h), IV, has been recommended to augment intravascular volume, thereby offsetting the hypotensive effects of anesthetic agents, and to maintain the perfusion of vital organs.[12] Increased **antidiuretic hormone (ADH)** concentrations develop secondary to anesthesia and surgery, which can contribute to oliguria and anuria.[13,14] Fluid therapy is important to maintain urine production during the perioperative period when plasma ADH concentrations can be in excess of those associated with maximal antidiuresis.[14]

Absolute blood volume deficits are common in surgical patients, and potential causes include preoperative withholding of food and water, blood loss, drying of body tissues, loss into body cavities and the interstitial space, and insensible fluid losses such as develop because of dry inhaled anesthetic gases. Patients undergoing nonelective surgeries often still have replacement requirements that have not been completely corrected prior to surgery. Intraoperative fluid losses further compound preexisting fluid deficits that result from medical or surgical diseases. Perioperative fluid therapy, therefore, is vital to maintain SV and CO in these patients such that tissue perfusion is not compromised. Furthermore, surgical patients often

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have acid-base imbalance, electrolyte disorders, and colloid osmotic pressure changes, which are compounded by the effects of anesthetic drugs.[15] These abnormalities should be corrected prior to and during anesthesia to minimize anesthetic complications. Splanchnic hypoperfusion during anesthesia can lead to bacterial translocation and **systemic inflammatory response syndrome (SIRS)**.[16] Surgical patients often have degrees of SIRS, which causes capillary permeability changes that can result in the rapid loss of administered fluids from the intravascular compartment. Fluid therapy, therefore, needs to be regulated according to the needs of the patient.

Types of Fluids Used in the Perioperative Period

Crystalloids—Crystalloids are aqueous solutions that contain small particles that are osmotically active in body fluids and can pass through the capillary membrane. The tonicity of a fluid is the osmolality of the fluid in comparison with intracellular osmolality. Crystalloids can be divided into hypotonic solutions (eg, 5% dextrose in water), isotonic solutions (eg, lactated Ringer's solution), and hypertonic solutions (eg, hypertonic saline). Crystalloids can be further divided into replacement solutions and maintenance solutions that differ primarily in their electrolyte concentrations. Replacement crystalloid fluids are often referred to as balanced electrolyte solutions because they have electrolyte composition and tonicity similar to that of plasma. Replacement solutions are appropriate for expansion of plasma volume. Maintenance crystalloid solutions, conversely, have electrolyte concentrations that are appropriate to replace daily insensible and sensible electrolyte losses.

Crystalloid solutions equilibrate with the interstitial and intracellular fluid compartments.[17-19] Isotonic crystalloid solutions have the same osmolality as that of cells and therefore only expand the extracellular space. Dextrose in water (5%) is a hypotonic solution because the osmotically active dextrose molecules are metabolized to free water. Hypotonic solutions can be used as a carrier fluid for drugs and for replacing free-water deficits but are not suitable for intravascular or interstitial volume replacement. After hypertonic saline solution is administered IV, water is initially drawn from the intracellular and interstitial fluid compartments to the intravascular compartment, thus improving hydrostatic pressure.[20] Most of the administered sodium, however, subsequently moves into the interstitial compartment, resulting in increased tonicity of the interstitial fluid and further reduction of intravascular volume.[20] Appropriate volumes of isotonic crystalloids or colloids should be administered after hypertonic saline solution to maintain blood volume.[21]

During anesthesia, replacement solutions are generally used because they are isotonic and can be given rapidly into the intravascular compartment. Administration of glucose (5%) or 0.18% saline solution and 4% glucose has been associated with hyponatremia and decreased plasma osmolality.[12] Most replacement solutions contain a bicarbonate-equivalent agent to prevent dilution of plasma bicarbonate by the administered fluid, which can result in dilutional acidosis. Seventy-five percent of an infused balanced electrolyte solution or crystalloid solution will be redistributed into the extravascular space.[19] Thus, to replace blood loss with crystalloid solutions, 3 to 4 times the volume of blood lost needs to be replaced. In dogs, < 20% of infused crystalloid solution remains in the intravascular space after 2 hours, and only 10.9% remains in the intravascular space after 3 hours.[19,22] Crystalloids can also dilute plasma proteins and coagulation factors, reducing plasma oncotic pressure and increasing the risk of interstitial and intracellular edema.[23,24] When rapid administration of large amounts of crystalloid fluids is necessary for replacement of intravascular volume, addition of colloids to maintain colloid osmotic pressure will decrease the required volume of crystalloid to be infused (**Table 1**).

Table 1—Compositions of commonly used parenterally administered solutions*

Solution	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	Ca^{++} (mEq/L)	Mg^{++} (mEq/L)	Buffer (mEq/L)	Osmolality (mOsm/L)	COP (mm Hg)
Ringer's lactate solution[a]	130	4	109	3	—	Lactate 28	274	0
Ringer's solution[b]	147	4	156	4	—	—	310	0
Normosol-R[c]	140	5	98	—	3	Acetate 27 Gluconate 23	294	(0)
Normal saline (0.9% NaCl) solution	154	—	154	—	—	—	308	0
Dextrose 5% in water	—	—	—	—	—	—	252	(< 1)
Dextrose 2.5% in 0.45% saline solution	77	—	77	—	—	—	280	(< 1)
Plasma-Lyte A[d]	140	5	98	—	3	Acetate 27	294	0
Plasma-Lyte 148[e]	140	5	98	—	3	Acetate 27 Gluconate 23	294	(0)
6% dextran 70, 0.9% NaCl[f] solution	154	—	154	—	—	—	310	62
Oxypolygelatin[g]	145	—	100	2	—	—	200	45–47
Hetastarch[h]	154	—	154	—	—	—	309	33
Pentastarch[i]	154	—	154	—	—	—	326	25

*Source: references 25–28 and footnotes a–i.
COP= Colloid osmotic pressure.
Figures in parentheses are extrapolated from published data. [a-i]Superscripts refer to footnotes.

Colloids—Colloid solutions are aqueous solutions that contain large particles that do not normally pass through capillary membranes and some smaller, more diffusable particles. The large, nondiffusable particles exert oncotic pressure that opposes the movement of water from the intravascular space to the interstitium. Colloid solutions, therefore, primarily replenish the intravascular fluid compartment. Colloids can be divided into natural colloids (eg, albumin) and synthetic colloids (eg, dextrans, gelatins, and hydroxyethyl starch preparations). The oncotic effect, method of excretion, and half-life of a synthetic colloid are determined by its molecular structure and molecular weight. Colloids are eliminated from the intravascular space by glomerular filtration, extravasation, storage in tissues, and via the gastrointestinal tract.

Colloids restore microcirculatory perfusion more effectively than crystalloids, with lower volume of required fluid and lower risk of fluid overload during fluid replacment.[17] Colloids are indicated when crystalloids alone are insufficient to maintain oncotic pressure or if a patient requires rapid volume replacement with less redistribution to the interstitial space. Such situations include increased capillary permeability and hypoproteinemia (total protein < 3.5 g/dL or albumin < 1.5 g/dL) and diseases that result in SIRS. In anemic states (PCV < 25 to 30%), synthetic colloids can be used in conjunction with packed RBC, or whole blood to increase plasma oncotic pressure. Administration of a hyperoncotic synthetic colloid would be expected to increase blood volume to a greater degree than would whole-blood administration alone (Table 1). Further indications for colloids include moderate to severe hypovolemic shock in which enormous volumes of crystalloids are required to maintain intravascular volume, hypovolemic patients with cerebral or pulmonary edema, and patients with third-space losses. Crystalloids are usually administered concurrently with colloids to replenish the interstitial and intracellular fluid compartments, but the crystalloid dose should be decreased by 40 to 60% to prevent a large increase in intravascular hydrostatic pressure and interstitial edema.

The potential disadvantages of colloids include circulatory overload, coagulopathies, anaphylactic reactions, and hyperosmotic renal dysfunction.[29-31] Prevalence of anaphylactic reactions to colloid administration in humans varies from 0.02 to 0.84%, with signs of adverse reactions including hypotension, urticaria, respiratory compromise, pulmonary edema, and gastrointestinal disturbances.[29] Colloids should be used cautiously in patients with oliguric or anuric renal failure, congestive heart failure, or pulmonary edema, and are contraindicated in patients with severe coagulopathy. When large volumes of synthetic colloids are administered to a patient, close attention to surgical hemostasis is indicated because of an increase in microcirculatory flow and the possible effects of the colloid on coagulation. In this situation, administration of fresh or fresh frozen plasma may be required to provide coagulation factors. Colloids can affect coagulation via direct effects on platelets and the coagulation cascade or via hemodilution. Administration of desmopressin can be used to increase von Willebrand's factor in order to ameliorate the induction of acquired von Willebrand's disease by hetastarch.[32] If patients become hyperoncotic from colloid administration, the Starling forces that drive glomerular filtration can be altered such that oliguric acute renal failure can result.[31]

In animals with hypovolemic or distributive shock, half to the entire daily maximum dose of a synthetic colloid can be administered to dogs as a rapid IV bolus to induce a more rapid effect on intravascular volume. Contraindications to bolus administration of colloids include hemorrhage in a closed cavity, cardiac disease, and trauma to the head. Intraoperative hemorrhage can be treated with an IV bolus of colloid, although RBC are preferred if the PCV decreases to < 25 to 30%. Incremental low-volume boluses of colloid should be administered during an interval of 15 to 30 minutes in cats to prevent fluid overload.

Dextrans—Dextrans are mixtures of glucose polymers and are available as preparations with a low molecular weight (dextran 40)[j-m] or high molecular weight (dextran 70[f,n,o] and dextran 75[p,q]). Dextran 70 is used more commonly in veterinary patients than is dextran 40 and is available as a 6% solution, in 0.9% saline solution, or 5% dextrose in water. The duration of intravascular expansion for dextran is approximately 24 hours; however, intravascular volume expansion decreases exponentially after administration and is only 0 to 20% of the infused volume after 24 hours.[33] An initial increase in plasma volume 1.38 times the volume of dextran 70 infused has been reported.[33] Potential adverse effects of dextran administration include antithrombotic effects, acute renal failure with dextran 40, anaphylaxis, and coagulopathies.[29,34-36] Mechanisms of dextran-induced coagulopathies include platelet coating by the dextran macromolecules, precipitation of coagulation factors, increased fibrinolytic activity, and decreased functional von Willebrand factor.[29,34] In clinically normal dogs, administration of dextran 70 (20 mL/kg [9.0 mL/lb], IV) during 30 or 60 minutes induces minimal hemostatic abnormalities but may precipitate bleeding in dogs with marginal hemostatic function.[34] Dextrans can interfere with the cross-matching of blood because of cross-linking and rouleaux formation of RBCs. A dextran dose of 10 to 20 mL/kg/d (4.5 to 9.0 mL/lb/d), IV, for dogs and 5 to 10 mL/kg/d (2.3 to 4.5 mL/lb/d), IV, for cats has been suggested.[37-39] Boluses of up to 20 mL/kg, IV, may be given to dogs to combat severe hypovolemic states.[39]

Gelatins—Gelatins are modified bovine collagens, and repeated infusions are required because of their short plasma half-life. Presently, only oxypolygelatin[g] is available for veterinary use in the United States. Oxypolygelatin is available as a 5.6% suspension in sodium chloride with a mean molecular weight of 30 kd. The reported elimination half-life of oxypolygelatin in humans is 2 hours.[40] A dose of 5 mL/kg, IV, titrated to effect up to a maximum total dose of 15 mL/kg, IV, for oxypolygelatin has been suggested.[39] Concurrent crystalloid administration is recommended with oxypolygelatin because of the large fluid shift from the interstitial compartment and

because of its diuretic effect secondary to the excretion of small gelatin molecules. Potential adverse effects associated with the administration of gelatins include anaphylaxis, dilutional coagulopathy, inhibition of platelet aggregation, and hypocalcemia.[29,41] Of the synthetic colloids available for veterinary use, gelatins appear to have the least detrimental effects on coagulation.[42,43] Gelatins or plasma should therefore be considered in preference to dextrans and hydroxyethyl starches in patients with coagulopathies or von Willebrand's disease.

Hydroxyethyl starch preparations—Hydroxyethyl starch preparations are derivatives of a branched starch compound called amylopectin. Available hydroxyethyl starch preparations include 2 forms of hetastarch[h,r] and pentastarch.[i] Hetastarch, available as a 6% solution, is the largest of the available synthetic colloids, with a mean molecular weight of 450 kd. Hetastarch is effective at increasing colloid oncotic pressure, and because of lower expense, compared with plasma, it is used more commonly for maintenance of oncotic pressure in veterinary patients. Despite great variation in the magnitude of plasma volume expansion, hetastarch is an effective volume expander, with volume expansion and replacement effects comparable to that of albumin.[44] The duration of intravascular expansion for hetastarch is 12 to 48 hours; however, intravascular volume expansion decreases exponentially after administration and is only 5 to 26% of the infused volume at 24 hours.[33] Hetastarch also reverses the effects of free radicals on microvascular permeability during reperfusion injury.[45] Hetastarch is administered slowly at a dose of 10 to 20 mL/kg/d, IV, (0.4 to 0.8 mL/kg/h [0.18 to 0.36 mL/lb/h], IV, **continuous rate infusion [CRI]**) in dogs, although boluses of half to the entire recommended daily dose can be used in patients with higher colloid requirements.[37,38] A dose of hetastarch for cats of 5 to 10 mL/kg, IV (0.2 to 0.4 mL/kg/hr [0.09 to 0.18 mL/lb/hr] IV, CRI) has been suggested.[38] Furthermore, small volume increments of 5 mL/kg, IV, given slowly during 5 to 15 minutes have been recommended in cats with higher colloid requirements.[39] At Colorado State University Veterinary Teaching Hospital, CRI dose rates used clinically for hetastarch are 1.0 to 2.0 mL/kg/h (0.45 to 0.9 mL/lb/h), IV, in dogs and 0.5 to 1.0 mL/kg/h (0.2 mL to 0.45 mL/lb/h), IV, in cats. Potentially adverse effects of hetastarch administration include anaphylaxis, hyperosmotic renal dysfunction, prolonged prothrombin, partial thromboplastin, and activated clotting times, dilutional coagulopathy, decreased platelet counts, decreased factor VIII function, and acquired von Willebrand's disease.[29,30,46-49] The detrimental effects of hetastarch on coagulation are more severe when higher doses (> 25% of recipient blood volume) are used.[49]

Pentastarch[i] is available as a 10% solution with a mean molecular weight of 280 kd. The reported rate of elimination of pentastarch is faster than for hetastarch, and it has less effect on coagulation parameters.[50,51] In 1 study, within 30 minutes of infusion, administration of 500 mL of pentastarch expanded plasma volume by 700 mL.[52] Dose rates that have been suggested for pentastarch are 10 to 25 mL/kg/d (4.5 to 11.4 mL/lb/d), IV, in dogs and 5 to 10 mL/kg/d, IV, in cats.[38]

Blood products—Blood products include fresh and stored whole blood, packed RBCs, fresh plasma, fresh frozen plasma, stored plasma, cryosupernatant, cryoprecipitate, and platelet-rich plasma. Conditions requiring blood component therapy include anemia, hypoalbuminemia, coagulopathies, **disseminated intravascular coagulation (DIC)**, SIRS, life-threatening thrombocytopenia, and acute hemorrhage.

Stored or frozen plasma—Stored or frozen plasma can be used to provide plasma proteins, in particular albumin. Albumin has a molecular weight of 69 kd and provides 75% of plasma oncotic pressure. Stored plasma is not used in routine fluid management of a patient when colloids and crystalloids are efficacious because of the cost of harvesting and storing plasma, the volumes required in replacement therapy, the relatively rapid disappearance of albumin from the vascular space, and the potential for disease transmission, anaphylaxis, and hypocalcemia.[29] According to the equation used by Hardin et al,[53] approximately 43 mL/kg (20 mL/lb) of plasma is required to increase the plasma albumin concentration by 5 g/L. Albumin has several functions in addition to exerting an osmotic effect, including binding and transport of drugs, hormones, metals and enzymes, free radical scavenging, and binding of inflammatory mediators. With substantial hypoalbuminemia (< 1.5 to 2.0 g/dL), therefore, plasma transfusion has been recommended as part of the colloid therapy to replenish depleted albumin.[54,55] Stored plasma is generally administered at a dose rate of 10 mL/kg, IV, during 4 to 6 hours. Stored plasma contains diminished quantities of factor V and factor VIII, but also contains the stable vitamin K-dependent factors II, VII, IX, and X.[56,58]

Fresh or fresh frozen plasma—Fresh or fresh frozen plasma is a source of albumin and also contains fibronectin, alpha-macroglobulin, antithrombin III, antitrypsin, and coagulation factors.[59-64] Fresh or fresh frozen plasma is indicated in patients with SIRS, DIC, coagulopathies, and when serum albumin is < 2.0 g/dL. Cross-matching is not required prior to plasma transfusions, although urticaria and angioneurotic edema secondary to type 1 hypersensitivity can develop because of reactions to plasma antigens. Performing a minor cross match between the recipient's RBCs and the donor's plasma can be used to predict a plasma transfusion reaction. Fresh or fresh frozen plasma is generally administered at a dose rate of 10 mL/kg, IV, during 4 to 6 hours. In patients with life-threatening coagulopathy, however, plasma can be administered as quickly as possible without inducing fluid overload.

Packed RBC, fresh whole blood, and stored whole blood—Red blood cells are required when the Hb content of blood has declined to a concentration at which blood oxygen content does not support tissue oxygenation. Patients undergoing anesthesia and surgery are less tolerant of low Hct because of depressed compensatory reflexes, myocardial depression, and anesthetic-induced vasodilation.[3,4,9] Maintaining a PCV of ≥ 25% has been recommended in surgical patients to maintain blood oxygen content.[37] Packed RBCs can be used for

transfusing patients with hemorrhagic shock, anemic patients with normovolemia, or anemic patients at risk of circulatory overload. Administration of whole blood is beneficial when patients require plasma proteins as well as RBCs. Fresh whole blood contains albumin, RBCs, coagulation factors, platelets, WBCs, and plasma proteins. Fresh whole blood is preferred in critically ill patients because stored blood and packed RBCs are extremely acidotic (pH can be as low as 6.5 after 37 days), compared with fresh whole blood.[65] Stored whole blood has decreased WBCs and platelets and decreased concentrations of factors V and VIII.[56,57,66-68] When large-volume blood loss occurs into the thorax or abdomen, autotransfusion can be considered. Autotransfused blood contains RBCs and albumin but no clotting factors. Potential problems associated with autotransfusion include coagulopathies, sepsis, microembolization of platelet aggregates, hemolysis and tumor embolization.[69-72]

Blood-typing and cross-matching should ideally be performed in all animals receiving a blood transfusion to prevent transfusion reactions because of incompatibilities in erythrocyte antigens. A universal donor that lacks all dog erythrocyte antigens except DEA 4 can be chosen for canine patients when time does not permit cross matching prior to blood transfusion. A first-time transfusion from any donor, however, is unlikely to cause an immediate transfusion reaction in dogs because they do not possess clinically important naturally occurring antibodies to other blood types, and 4 to 14 days are required for the recipient to produce antibodies against the donor cells.[73-75] In 1 study, all type B cats and 44% of type A cats possessed naturally occurring isoantibodies against the opposite RBC antigens at an agglutination titer of ≥ 2.[76] Hence, blood-typing of donor and recipient cats is recommended with all feline transfusions, and a major and minor cross match is recommended even in first-time blood transfusions. Type A cats with anti-B serum given mismatched blood will have a mild systemic reaction that causes a mean half-life of 2 days for the transfused cells.[77] Type B cats with anti-A serum given mismatched blood can develop a severe hemolytic reaction that shortens the lifespan of the transfused cells to 1 to 2 hours and potentially leads to death.[77]

The dose rate for whole blood and administration of packed RBCs is calculated from the following equation:

$$\text{Volume (mL) of blood required} = \frac{\text{PCV desired} - \text{PCV recipient}}{\text{PCV donor}} \times \text{BW} \times \text{BV}$$

where BW is body weight of the recipient (kg [lb]) and BV is blood volume of the recipient per kg (90 mL/kg [41 mL/lb] for dogs, 60 mL/kg [27 mL/lb] for cats).

Empirical dose rates for blood transfusions are 20 to 25 mL/kg (9 to 11 mL/lb), IV, for whole blood and 15 to 20 mL/kg, IV, for packed RBCs for dogs and 10 mL/kg, IV, for whole blood for cats. Another rule of thumb is that 1 mL of whole blood/lb will raise the recipient PCV by 1% (assuming a donor PCV of 40%). The calculated dose of blood is generally administered during 4 to 6 hours, unless the patient has life-threatening hemorrhagic shock, when whole blood can be administered as rapidly as possible to restore MAP to at least 60 mm Hg. In hemodynamically stable patients, the blood transfusion is delivered slowly at 0.25 to 1.0 mL/kg/h (0.11 to 0.45 mL/lb/h), IV, during the first 15 minutes, to observe for signs of a transfusion reaction that can include restlessness, salivation, vomiting, fecal and urinary incontinence, pruritis, weakness and collapse, pyrexia, urticaria, hypocalcemic tetany, tachycardia, dyspnea, and hypotension.[74,75,77,78] The rate can subsequently be increased to 2.5 to 5 mL/kg/h (1.1 to 2.3 mL/lb/h), IV, if no adverse reactions are observed, although it has been recommended that the rate of administration should be maintained at 0.5 to 1.0 mL/kg/h, IV, in patients with cardiac disease.[79]

Citrated blood products should not be administered through the same IV lines as calcium-containing products such as lactated Ringer's solution, because calcium will precipitate citrate in the anticoagulant.[80] Citrate toxicosis can occur when large volumes of blood are administered too rapidly or in patients with impaired liver function.[81,82] Citrate binding of blood calcium can lead to hypocalcemia, resulting in muscle tremors and cardiac dysrhythmias, and the adverse cardiovascular effects are potentiated by halothane.[81-83] Serum ionized calcium concentrations should be monitored when large volumes or rapid transfusions of blood are administered.

Oxygen-carrying fluids—Interest in oxygen-carrying fluids evolved because of the drawbacks associated with blood transfusions including the expense, need for cross matching, potential for disease transmission, limited availability of donor animals, and morbidity rates associated with transfusion reactions.[84,85] Acellular, oxygen-carrying solutions include free-Hb-based solutions, liposome-encapsulated Hb solutions, and perfluorochemicals.[86-88] **Hemoglobin-based oxygen carriers (HBOC)** combine the oxygen-carrying capacity of blood with the osmotic, storage, and stability properties of colloidal solutions.

Definitive recommendations regarding the use of oxygen-carrying solutions in small animals cannot be made without further evaluation of their hemodynamic effects. Hemoglobin solutions may improve tissue perfusion and oxygenation because of their easy penetration into the microcirculation and their right-shifted oxygen dissociation curve.[84] Other hemodynamic effects of Hb solutions include a vasopressor effect, an oncotic effect, and nitrous oxide-scavenging effects.[84] Potential indications for Hb solutions in veterinary medicine include resuscitation from shock and acute blood loss, treatment of brain injury, sepsis, chronic anemia, treatment and prevention of ischemia resulting from hypoperfusion, hemopoietic stimulation, and perioperative blood volume replacement.[84,89] During the perioperative period, Hb solutions may have value in replacing small volumes of lost blood, in providing oxygen-carrying capacity until a blood transfusion can be performed, or for use in patients with multiple antibodies against RBC antigens resulting from previous blood transfusions.

Sources of acellular Hb include outdated human blood, bovine Hb, and recombinant Hb.[89] Potential problems associated with Hb solutions include renal toxicosis, oxidative damage, reperfusion injury, hypertension, platelet activation, and impaired immune defense mechanisms.[90-95] Unmodified human Hb has a high oxygen affinity that prevents adequate release of oxygen to the tissues.[96] Modification of the Hb molecules has been developed to improve oxygen release, prolong intravascular half-life, decrease colloid osmotic activity, prevent renal toxicosis, and avoid antigenicity.[91,97]

Bovine Hb solution—Hemoglobin glutamer-200 (bovine)[s] is an ultrapurified polymerized bovine Hb in a modified lactated Ringer's solution with a pH of 7.8. It contains 13 g of bovine Hb/L and has an osmolality of 300 mOsm/kg. This product was approved by the FDA for veterinary use in dogs in 1998. The Pa_{O_2} when this Hb is 50% saturated is 36 mm Hg, which is slightly greater than that of Hb in RBCs, which facilitates the uptake and release of oxygen from the Hb molecule. The manufacturer's recommended dose is 30 mL/kg (14 mL/lb), IV, at a rate not to exceed 10 mL/kg/h (4.5 mL/lb/h). At Colorado State University, the dose used clinically is 10 to 15 mL/kg, IV, in dogs and 3 to 5 mL/kg (1.4 to 2.3 mL/lb), IV, in cats. It requires no cross-matching or blood-typing prior to use and has a 2-year shelf life at 20°C. The colloid osmotic pressure of the product is 43 mm Hg, which is greater than that of hetastarch.[25] After administration, patients should be closely monitored for signs of circulatory overload and pulmonary edema by use of frequent lung auscultation and measurement of central venous pressure. Direct measurement of Hb is recommended to monitor the effect of treatment, because the Hct will decrease because of hemodilution despite an improvement in the oxygen-carrying capacity of the blood. This product has the potential to interfere with chemical analyses because of its persistence in plasma and serum.[98] Transient discoloration of urine can develop after infusion because the kidneys clear a small portion of the product. Transient discoloration of mucous membranes and sclera from yellow to red can also develop for approximately 3 to 5 days after infusion.

Fluid Additives

Potassium—Hypokalemia is a common electrolyte disorder in surgical patients because many lost fluids contain potassium in excess of normal extracellular fluid. Furthermore, the kidney is an obligatory potassium excreter in its attempts to conserve sodium. Perioperative supplementation of fluids with potassium may cause inadvertent potassium toxicosis if a fluid bolus is given to correct hypotension. A safer method is to administer potassium during surgery as a CRI via a syringe pump up to a maximum rate of 0.5 mEq/kg/h (0.2 mEq/lb/h), IV. Guidelines for potassium supplementation of maintenance solutions have been reported.[99] The amount of potassium added should be adjusted according to blood pH, because acidemia will increase and alkalemia will decrease the apparent serum potassium concentration.[100]

Prior to anesthesia, hyperkalemia should be corrected by use of sodium chloride volume replacement and diuresis, and in more severe cases, by administration of dextrose and regular insulin. In emergency situations (eg, life-threatening bradycardia), 10% calcium chloride at 0.1 mL/kg, IV, 10% calcium gluconate at 0.5 to 1.5 mL/kg (0.23 to 0.68 mg/lb), IV, or sodium bicarbonate at 0.5 to 1 mEq/kg (0.23 to 0.45 mEq/lb), IV, may be administered to temporarily improve clinical signs. Clinical disorders of potassium homeostasis and therapeutic strategies have been reviewed elsewhere.[99] Correction of metabolic acidemia by administration sodium bicarbonate will induce transcellular relocation of potassium to the intracellular compartment and thereby lower serum potassium concentration.

Calcium—Calcium plays an important role in maintenance of physiologic homeostasis. In plasma, calcium is in ionized, protein-bound, and chelated forms.[101] Of these, the ionized portion is most important physiologically, and measurement of ionized calcium is preferable to total calcium concentration.[102] Anaerobic collection and handling of serum for ionized calcium estimation is essential and as for potassium ion, the measured value is influenced by pH (higher values in acidemic patients).[103] Use of heparin in blood samples can substantially reduce ionized calcium concentration.[104] Regulation of calcium within the body is a complex process involving the endocrine, digestive, musculoskeletal, and renal systems, making diagnosis and treatment of hypocalcemia and hypercalcemia challenging.

The causes of hypercalcemia have been reviewed and include pathologic and nonpathologic conditions.[105] Treatment is generally focused on the underlying cause. Hydration by use of 0.9% NaCl saline solution to promote diuresis is important in the short-term treatment of hypercalcemia, because dehydration reduces renal clearance of calcium. Loop diuretics can be used to increase calciuresis, and in refractory cases, administration of calcitonin may be necessary.[105]

Hypocalcemia is more common than hypercalcemia in the perioperative period. The cardiovascular, musculoskeletal, and CNS all have clinical signs attributable to hypocalcemia, which include muscle tremors or cramping, facial rubbing, stiff gait, behavioral changes, panting, lethargy, inappetence, pyrexia, tachycardia, polyuria, and polydypsia.[105] Hypocalcemia may contribute to poor patient outcome in the peri-anesthetic period. During anesthetic maintenance, a common cause of hypocalcemia is rapid administration of fluids and citrated blood products. This can cause depressed myocardial contractility and hypotension.[81-83] Acute hypocalcemia may be treated with slow IV administration of ≤ 15 mg of elemental calcium/kg (6.8 mg/lb), IV.[105] This may be followed with repeated doses or a CRI if necessary. It is important to note that a 10% calcium chloride solution contains 3 times the amount of elemental calcium contained in a 10% calcium gluconate solution. Hence, the dose of calcium chloride is a third lower than for calcium gluconate. Cardiovascular status must be closely monitored during IV administration of calcium because of the potential risk of dysrhythmias

associated with rapid infusion.[105] Hypocalcemia can be associated with hypomagnesemia and is often refractory to treatment with calcium until the magnesium deficiency is corrected.[106]

Magnesium—Critically ill patients have a high prevalence of concurrent magnesium and potassium deficiency.[107] In canine patients, an association between hypomagnesemia and cardiovascular disease, and hypokalemia and hypoalbuminemia has been identified.[108] Hypomagnesemia may inhibit the sodium-potassium ATP pump, resulting in a decrease in intracellular potassium concentration.[109] This can decrease the resting membrane potential of cardiac cells and increase excitability and cause predisposition to cardiac dysrhythmias.[110] An association between hypomagnesemia and dysrhythmias is documented in human patients, and magnesium infusion is recommended for the treatment of torsade de pointes, refractory ventricular tachycardia, refractory ventricular fibrillation, and supraventricular arrhythmias.[111-114] Magnesium supplementation for critically ill veterinary patients undergoing anesthesia, therefore, should be considered as a possible means to support cardiovascular function and to decrease the prevalence of dysrhythmias, especially in patients with underlying cardiovascular disease. Magnesium also decreases analgesic requirements in human patients undergoing elective abdominal surgery, possibly because of blockade of the N-methyl-D-aspartate receptor complex.[115]

Magnesium supplementation has been recommended if serum magnesium concentration is < 1.2 mg/dL.[116] Serum magnesium concentration, however, may be an inaccurate measurement of total body magnesium because serum magnesium represents < 1% of total body magnesium.[117] Renal function should be assessed before magnesium supplementation because a 50 to 75% reduction in magnesium dose is recommended during azotemia.[116] Treatment with magnesium can be achieved by supplementing crystalloid fluids at a rate of 0.75 to 1.0 mEq/kg/d (0.3 to 0.45 mEq/lb/d), IV, with daily monitoring of serum magnesium concentration.[116] If hypomagnesemia is suspected as a cause for life-threatening ventricular dysrhythmia, an IV bolus of 0.15 to 0.3 mEq/kg (0.07 to 0.14 mEq/lb), IV, can be given during 5 to 15 minutes.[116] A fixed-rate infusion of magnesium at 0.12 mEq/kg/min (0.05 mg/lb/min), IV, does not induce adverse hemodynamic effects in healthy dogs, up to a cumulative dose of 1.0 to 2.0 mEq/kg (0.45 to 0.9 mEq/lb), IV.[118] Magnesium chloride should not be added to calcium-containing solutions including Ringer's and lactated Ringer's solutions. Signs of magnesium toxicity include hypocalcemia, hypotension, atrioventricular and bundle branch blocks, and respiratory muscle weakness.[118,119] Magnesium overdose can be treated with IV administration of calcium gluconate as a bolus (50 mg/kg [22.7 mg/lb], IV), followed by a CRI of 10 mg/kg/h, IV.[116] Patients with refractory hypokalemia should receive supplemental magnesium, because the hypokalemia may not be correctable until the magnesium deficiency is rectified.[120]

Bicarbonate—Acid-base imbalance during anesthesia can result from metabolic or respiratory abnormalities, or both. Maintenance of a relatively constant body pH is important for physiologic homeostasis and optimum function of cellular enzyme systems. Hypoventilation and hyperventilation cause respiratory acidosis and respiratory alkalosis, respectively. In anesthetized patients, the $PaCO_2$ should be maintained within reference range (37 to 43 mm Hg) to prevent respiratory acidosis. Metabolic acidosis is treated by reversing the underlying cause and by administering IV fluid therapy. If the inciting cause is corrected, volume restoration will enable most animals to correct their own acid-base imbalance by renal regulation and by formation of bicarbonate from lactic acid mobilized from tissues. The base deficit of a patient is calculated by titrating the blood to pH 7.4 with a strong acid or base or derived from a nomogram if pH, $PaCO_2$, and Hb are known. The dose of bicarbonate to be given in acidemic patients refractory to fluid therapy or patients with a substantial acidemia (pH < 7.2) can be calculated by the following equation:

$$\text{Bicarbonate required (mEq)} = \text{base deficit} \times \text{body weight (kg)} \times 0.3$$

Initially, 25 to 50% of this calculated dose is administered by adding the bicarbonate to the IV fluids or by slow IV injection during 20 to 30 minutes. Alternatively 1, 3, or 5 mEq of sodium bicarbonate/kg (0.5, 1.4, or 2.3 mEq/lb), IV, may be administered if the acidemia is perceived to be mild, moderate, or severe, respectively.

Glucose—Glucose can be added to crystalloids to avoid hypoglycemia in susceptible surgical patients. Such patients include pediatric patients, patients with low body weight, and patients with absolute or relative insulin overdose, insulinoma, liver failure, portosystemic shunts, or septic shock. Routine supplementation of crystalloid fluids with dextrose for perioperative fluid therapy is not recommended because hyperglycemia may induce osmotic diuresis and subsequent dehydration.[121]

Dextrose is added to a crystalloid solution to achieve a final concentration of 2.5 or 5% dextrose depending on the degree of hypoglycemia. The amount of 50% dextrose added to crystalloid solution to achieve an exact final concentration of 2.5 or 5% is calculated by use of the following equation:

$$V_1 = (V_2 \times S_2)/S_1$$

where V1 is the volume of concentrated dextrose solution, V2 is the volume of the final solution, S2 is the concentration of dextrose (%) in the final solution, and S1 is the strength of the concentrated (%) dextrose solution.

A rule of thumb that can be used is to add 50 mL of 50% dextrose solution to 1,000 mL of crystalloid solution or 5 mL of 50% dextrose solution to 100 mL of crystalloid solution to achieve a final dextrose concentration of approximately 2.5%. In most patients with severe hypoglycemia (≤ 60 mg/dL) and clinical signs, an immediate IV bolus of 1 mL/kg of 50% dex-

trose diluted with physiologic saline solution is recommended prior to beginning an infusion of dextrose. This should transiently increase blood glucose concentration to approximately 100 mg/dL. When supplementing IV fluids with dextrose, blood glucose concentration should be monitored to maintain concentration in the range of 70 to 120 mg/dL.

[a]Lactated Ringer's injection, Abbott Laboratories, Abbott Park, Ill.
[b]Ringer's injection, Abbott Laboratories, Abbott Park, Ill.
[c]Normosol-R, Abbott Laboratories, Abbott Park, Ill.
[d]Plasma-Lyte A, Baxter Healthcare Corp, Deerfield, Ill.
[e]Plasma-Lyte 148, Baxter Healthcare Corp, Deerfield, Ill.
[f]6% Gentran 70, Baxter Healthcare Corp, Deerfield, Ill.
[g]Rapidvet Plasm-Ex, DMS Laboratories, Flemington, NJ.
[h]Hespan, B. Braun Medical Inc, Irvine, Calif.
[i]Pentaspan, Du Pont Pharmaceuticals, Wilmington, Del.
[j]Dextran 40, B. Braun Medical Inc, Irvine, Calif.
[k]10% Gentran 40, Baxter Healthcare Corp, Deerfield, Ill.
[l]10% LMD, Abbott Laboratories, Abbott Park, Ill.
[m]Rheomacrodex, Medisan, Parsippany, NJ.
[n]Dextran 70, B. Braun Medical Inc, Irvine, Calif.
[o]Macrodex, Medisan, Parsippany, NJ.
[p]Dextran 75, Abbott Laboratories, Abbott Park, Ill.
[q]Gentran 75, Baxter Healthcare Corp, Deerfield, Ill.
[r]Hetastarch 6% in 0.9% injection, Baxter Healthcare Corp, Deerfield, Ill.
[s]Oxyglobin solution, Biopure Corp, Cambridge, Mass.

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