Massive transfusion in dogs: 15 cases (1997-2001)

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Objective—To determine clinical characteristics of dogs that received massive transfusion and identify the underlying diseases, complications, and outcomes.

Design—Retrospective study.

Animals—15 dogs.

Procedure—Medical records of dogs receiving a massive blood transfusion were evaluated for transfusion volume, underlying disease process or injury, benefits and complications of transfusion, and outcome. A massive transfusion was defined as transfusion of a volume of blood products in excess of half the patient’s estimated blood volume (90 ml/kg [40 ml/lb]) in a 24-hour period or transfusion of a volume of blood products in excess of half the patient’s estimated blood volume in a 3-hour period.

Results—Six dogs had intra-abdominal neoplasia resulting in hemobadmen, 3 had suffered a traumatic incident resulting in hemobadmen, and 6 had nontraumatic, non-neoplastic blood loss. Mean volumes of packed RBC and fresh-frozen plasma administered were 66.5 ml/kg (30 ml/lb) and 22.2 ml/kg (10 ml/lb), respectively. All dogs evaluated developed low ionized calcium concentrations and thrombocytopenia. Transfusion reactions were recognized in 6 dogs. Four dogs survived to hospital discharge.

Conclusions and Clinical Relevance—Results suggest that massive transfusion is possible and potentially successful in dogs. Predictable changes in electrolyte concentrations and platelet count develop. (J Am Vet Med Assoc 2002;220:1664–1669)

In recent years, blood transfusion of veterinary patients has become commonplace. Transfusions may consist of whole blood or blood components, such as packed RBC (PRBC) or fresh-frozen plasma (FFP). Red blood cell transfusions are typically given to correct anemia resulting from hemorrhage, RBC destruction, or inadequate erythropoiesis. Plasma transfusions are indicated to replace coagulation factors and occasionally to treat hypoproteinemia. Retrospective reviews of transfusion practices in veterinary medicine have been published, and in these reviews, the volume of PRBC given to dogs receiving transfusions was typically 10 to 19 ml/kg (4.5 to 8.6 ml/lb). Acute blood loss, hemolysis, coagulopathy, and bone marrow failure were the most common indications for transfusion. Survival rates of dogs undergoing transfusion ranged from 47 to 61%, with most dogs dying of the underlying disease process, rather than an inability to meet blood transfusion requirements.

In human medicine, transfusion of very large amounts of blood is occasionally warranted. Massive transfusion, the term coined for this clinical situation, has been defined as transfusion of a volume of whole blood or blood components that is greater than the patient’s estimated blood volume within a 24-hour period. Other definitions have included replacement of half the patient’s estimated blood volume in 3 hours, administration of blood products at a rate of 1.5 ml/kg/min over a period of 20 minutes, or the replacement of 150% of the patient’s blood volume irrespective of time. Given the severity of injuries and disease processes that cause near exsanguination, it should not be surprising that individuals who receive massive transfusion experience numerous complications and a high mortality rate. Some of the reported complications include electrolyte disturbances, coagulation defects, hypothermia, alterations in acid-base status, impaired wound healing, acute lung injury, various transfusion reactions, and transmission of infectious diseases.

Massive transfusion imposes a substantial drain on blood banking resources, with a select few patients consuming a large percentage of a hospital’s blood supply. To date, there have been no reports in the veterinary literature on massive transfusion, and survival rate following this type of blood product expenditure is not known. The purposes of the study reported here were to determine clinical characteristics of dogs that received massive transfusion and identify the underlying diseases, complications, and outcomes associated with massive transfusion in these dogs.

Criteria for Selection of Cases

The Tufts University hospital transfusion log for January 1997 through June 2001 was reviewed, and dogs and cats receiving a substantial volume of blood products relative to body size (approx 1 unit/5 kg [1 unit/11 lb]) were identified. Medical records of these animals were subsequently evaluated to determine whether they met the criteria for massive transfusion. For purposes of this study, massive transfusion was defined as transfusion of a volume of blood products in excess of the patient’s estimated blood volume (90 ml/kg [40 ml/lb] for dogs and 66 ml/kg [30 ml/lb] for cats) in a 24-hour period or transfusion of a volume of blood products in excess of half the patient’s estimated blood volume in a 3-hour period. Blood products were defined as whole blood, PRBC, or FFP. Blood products were prepared from voluntary donors, stored, and transfused according to standard techniques, as described.

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Procedures

Data collected from the medical records included signalment, weight, results of the initial physical examination, and underlying disease or injury. The volume and type (PRBC, FFP) of blood products transfused during the massive transfusion and during the entire hospital stay and the volume and type of additional fluids (crystalloids, colloids) administered IV were also recorded.

Results of serial measurements of PCV, total solids concentration, electrolyte concentrations, lactate concentration, blood-gas values, and various coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [APTT], and platelet count) were recorded. Electrolyte concentrations that were measured included sodium (Na+), chloride (Cl–), potassium (K+), ionized calcium (iCa++), and ionized magnesium (iMg++). Electrolyte and lactate concentrations and blood-gas values were measured with a point-of-care testing instrument. Recorded values for pH, iCa++ concentration, iMg++ concentration, and rectal temperature were the nadir values reported in the medical record during the massive transfusion period. Ionized calcium concentration was classified as extremely low if values were < 0.70 mmol/L. Recorded values for K+ concentration were the highest values documented during the transfusion period.

Laboratory values obtained prior to massive transfusion were compared with those obtained after. Because the timing of follow-up laboratory testing was at the discretion of the attending clinician, post-transfusion values included those obtained between the initiation of the transfusion but within 12 hours of the end of massive transfusion.

Medical records were evaluated for evidence of transfusion reactions. Animals considered to have had a transfusion reaction if rectal temperature increased > 0.6 C (1 F) above the upper reference limit or if vomiting, tachycardia, dyspnea, salivation, urticaria, angioedema, or hemolysis were reported to have developed during the transfusion.

Other data retrieved from the medical records included results of serial measurements of rectal temperature and whether a surgical procedure was performed. Outcome and number of days to discharge or death were calculated. Any animal that was discharged from the hospital was considered to have survived.

Statistical analyses—Pre- and posttransfusion values for iCa++, iMg++, and K+ concentrations and pH were compared with a Wilcoxon matched-pairs signed-ranks test. Values of P < 0.05 were considered significant. All analyses were performed with computerized software.

Results

During the period from January 1997 through June 2001, a total of 3,503 units of blood products were transfused. After review of the hospital transfusion log, 46 cases were selected for further review of their medical records. Of these, 15 dogs, but no cats, met the criteria for inclusion in the study. Nine dogs were transfused with a volume of blood products in excess of their calculated blood volume within 24 hours. An additional 6 dogs were transfused with a volume of blood products in excess of half their calculated blood volume within 3 hours. Many of the 9 dogs that fulfilled the 24-hour transfusion criterion also received blood products equal to half their blood volume within 3 hours, including 2 dogs that received an entire blood volume in < 3 hours.

There were 3 Labrador Retrievers, 2 Golden Retrievers, 2 Weimaraners, 3 spaniels (2 Springer Spaniels and 1 Brittany Spaniel), 1 Great Pyrenees, 1 pit bull-type dog, 1 Pug, 1 Bichon Frise, and 1 Miniature Pinscher. Mean ± SD age was 6.9 ± 3.65 years (range, 2 to 15 years). There were 10 neutered males and 5 spayed females. Mean weight was 27.12 ± 13.92 kg (59.66 ± 30.62 lb; range, 3.1 to 45 kg [6.82 to 99 lb]).

Illnesses and injuries in animals that received massive transfusion included abdominal neoplasm with resultant hemoabdomen (n = 6), traumatic hemoabdomen (3), gastric dilatation-volvulus (2), gastrointestinal hemorrhage (3), and septic peritonitis with severe intra-abdominal hemorrhage because of adhesions and hypoproteinemia following surgery 3 days earlier for a gastrointestinal foreign body (1). Of the 6 dogs with hemorrhage related to neoplasia, tissue diagnoses included splenic hemangiosarcoma (n = 2), anaplastic sarcoma, adrenocortical carcinoma, anaplastic carcinoma, and renal transitional cell carcinoma. Of the 3 dogs with gastrointestinal hemorrhage, 1 had hemorrhage associated with ulceration secondary to naproxen ingestion, 1 had hemorrhage associated with gastric ulceration that developed 1 week after gastropathy for gastric dilatation-volvulus, and 1 had severe diffuse hemorrhage secondary to thrombocytopenia.

Blood transfusion requirements—Mean volume of PRBC administered was 66.5 ml/kg (30 ml/lb; range, 23.2 to 113 ml/kg [15 to 51 ml/lb]); mean volume of FFP administered was 22.2 ml/kg (10 ml/lb; range, 6.5 to 73 ml/kg [3 to 33 ml/lb]). This represented a total of 115 units of blood products for the 15 dogs in the study. Mean volume of blood products administered, as a percentage of calculated blood volume, was 99% (range, 59 to 141%). Mean transfusion time was 8.5 hours (range, 1 to 24 hours).

Ionized calcium concentration—Mean ± SD serum iCa++ concentration prior to transfusion was 1.19 ± 0.13 mmol/L (n = 13; reference range, 1.2 to 1.4 mmol/L). Ionized calcium concentrations before and after transfusion were available for 10 dogs. For these dogs, mean iCa++ concentration prior to transfusion (1.17 ± 0.14 mmol/L) was significantly (P = 0.005) higher than mean concentration after transfusion (0.89 ± 0.19 mmol/L). Ionized calcium concentration was less than the lower reference limit following massive transfusion in all 10 dogs and was extremely low (< 0.70 mmol/L) in 2. One dog that required massive transfusion because of traumatic hemoabdomen had persistent intra-operative hypotension; this dog was treated for hypocalcemia with calcium gluconate (50 mg/kg [23 mg/lb], IV).
Ionized magnesium concentration—Mean ± SD serum iMg²⁺ concentration prior to transfusion was 0.45 ± 0.17 mmol/L (n = 12; reference range, 0.23 to 0.43 mmol/L). Ionized magnesium concentrations before and after transfusion were available for 9 dogs, and changes in iMg²⁺ concentrations in these dogs paralleled changes in iCa²⁺ concentrations. Mean iMg²⁺ concentration prior to transfusion (0.48 ± 0.19 mmol/L) was significantly (P = 0.007) higher than mean concentration after transfusion (0.30 ± 0.13 mmol/L).

Sodium and chloride concentrations—Serum Na⁺ and Cl⁻ concentrations prior to transfusion were available for 15 dogs; concentrations after transfusion were available for 10 dogs. Significant differences between concentrations before and after transfusion were not detected. Mean ± SD serum Na⁺ concentrations before and after transfusion were 144 ± 7 and 145 ± 6 mEq/L, respectively (reference range, 147 to 154 mEq/L). Mean serum Cl⁻ concentrations before and after transfusion were 114 ± 9 and 119 ± 7 mEq/L, respectively (reference range, 109 to 120 mEq/L).

Potassium concentration—Serum K⁺ concentration prior to transfusion was available for 15 dogs; concentration after transfusion was available for 10 dogs. Mean ± SD serum K⁺ concentration before transfusion (4.3 ± 1 mEq/L; reference range, 3.8 to 5.4 mEq/L) was not significantly different from mean concentration after transfusion (4.2 ± 2 mEq/L). One patient was hyperkalemic prior to massive transfusion (7.6 mEq/L). Two patients were hyperkalemic after transfusion (8.1 and 5.8 mEq/L); both had concurrent metabolic acidosis (pH 7.12 and 7.33, respectively), but the hyperkalemia was in excess of that predicted given the degree of acidosis. One of these dogs was also oliguric (urine output, < 1 ml/kg/h). Both were normokalemic prior to transfusion (3.6 and 4.8 mEq/L, respectively).

Blood-gas values—Results of blood-gas analyses performed prior to transfusion were available for 13 dogs; results of analyses performed after transfusion were available for 11 dogs. Mean ± SD blood pH was 7.156 ± 0.316 (range, 6.280 to 7.456) prior to transfusion and 7.231 ± 0.173 (range, 6.886 to 7.423) after transfusion. Blood pH was decreased after transfusion in 2 patients, both of which died shortly thereafter, and was increased or unchanged in the remaining 9 dogs. Blood pH values prior to transfusion in 3 of the 4 dogs that survived that developed hemolysis also had facial swelling; a second dog that developed hemolysis had a transient fever.

Lactate concentration—Serum lactate concentration was measured prior to transfusion in 11 dogs and after transfusion in 10. Mean ± SD serum lactate concentrations were 10.4 ± 6.1 mmol/L (range, 0.6 to 18.5 mmol/L) before transfusion and 8.7 ± 5.2 mmol/L (range, 0.5 to 18.6 mmol/L) after transfusion. Serum lactate concentrations prior to transfusion in 3 of the 4 dogs that survived that developed hemolysis were 3.8, 2.8, and 13.1 mmol/L.

Coagulation parameters—Results of tests of hemostatic function, including platelet count, PT, or APTT, were available for 12 dogs. Platelet counts prior to transfusion were available for 5 patients; 2 of these dogs had normal platelet counts, and 3 had thrombocytopenia with platelet counts between 100 and 175 X 10⁵/μL. Platelet counts during or after transfusion were available for 5 dogs, and all 5 had thrombocytopenia, with platelet counts between 50 and 100 X 10⁵/μL. Platelet counts before and after transfusion were available for only 2 dogs; both had mild thrombocytopenia before transfusion and moderate thrombocytopenia after transfusion (173 and 64 X 10⁵/μL, respectively, for a dog with gastrointestinal bleeding and 124 and 56 X 10⁵/μL, respectively, for a dog with hemoabdomen).

Prothrombin time and APTT before transfusion were available for 4 dogs and were normal in 3; times were 100 to 150% prolonged in the fourth dog. Prothrombin time and APTT were available during or after transfusion in 10 dogs and were normal in 3 dogs, 100 to 150% prolonged in 4, and > 150% prolonged in 3. Prothrombin times and APTT were available before and after transfusion for 2 dogs and were within reference limits at both times in both dogs. Two dogs with PT and APTT prolonged 100 to 150% survived. No animal with a > 150% prolongation of the PT and APTT survived.

Rectal temperature—Hypothermia was detected in 9 of the 15 dogs on arrival and in 9 of 13 dogs for which rectal temperatures after transfusion were available. For the 9 dogs with hypothermia after transfusion, rectal temperature ranged from 34.2 to 37.2 C (93.6 to 98.9 F; mean ± SD, 35.5 ± 0.89 C [95.97 ± 1.61 F]). There was no apparent association between nadir rectal temperature and outcome, as 2 of the 4 dogs that survived had temperatures among the lowest for the group (< 35.6 C [96 F]).

Adverse reactions—Transfusion reactions were recorded in 6 of 13 dogs. These consisted of transient fever (n = 3), vomiting (1), facial swelling (1), and delayed hemolysis (3). One of the 3 dogs that developed hemolysis also had facial swelling; a second dog that developed hemolysis had a transient fever.

Treatment and outcome—Twelve dogs underwent surgery; the other 3 were treated medically only. The dog with severe diffuse hemorrhage secondary to thrombocytopenia received only medical treatment and survived to discharge. The dog with gastrointestinal hemorrhage secondary to naproxen toxicity only received medical treatment and died. A dog with traumatic hemoabdomen died before it could be adequately stabilized for surgery.

Four of the 15 dogs survived to discharge, including a 3-year-old Miniature Pinscher with traumatic hemoabdomen and diaphragmatic hernia, a 7-year-old Bichon Frise with gastrointestinal hemorrhage secondary to thrombocytopenia, a 10-year-old Weimaraner with gastric ulceration 1 week after undergoing surgery for gastric dilatation-volvulus, and a 5-year-old neutered male Labrador Retriever with hemoabdomen secondary to renal transitional cell carcinoma. Of the remaining 11 dogs, 10 died and 1 was euthanatized following cardiopulmonary arrest and resuscitative efforts. Mean duration of hospitalization was 4.6 days.
from iCa2+. Hypocalcemia has been reported to resolve of sodium bicarbonate, and rapid infusion of fluids free alkalosis, marked hyperphosphatemia, administration metabolized by the liver, but metabolism of citrate quickly following transfusion, as citrate is rapidly

Signs of hypomagnesemia tend to mimic those hypomagnesemia in patients receiving massive transfusion, with 46% of patients having severe hypocalcemia. Hypocalcemia most likely arises as a result of the citrate that is added to blood products as an anticoagulant. Once in the body, the citrate binds rapidly to calcium and magnesium, decreasing iCa2+ and iMg2+ concentrations. Low iCa2+ concentrations may also result from metabolic alkalosis, marked hyperphosphatemia, administration of sodium bicarbonate, and rapid infusion of fluids free from iCa2+. Hypocalcemia has been reported to resolve quickly following transfusion, as citrate is rapidly metabolized by the liver, but metabolism of citrate may take place more slowly in patients with liver disease or hypothermia. Treatment is generally indicated only in patients with clinical signs of hypocalcemia, such as hypotension, muscle tremors, or arrhythmias. Clinical signs that could have been consistent with hypocalcemia were identified in only 1 of the dogs in the present study, which was treated with calcium gluconate because of intraoperative hypotension.

In the present study, serum iMg2+ concentration was significantly decreased after transfusion, compared with concentration before transfusion. Decreases in iMg2+ concentration following massive transfusion are believed to result from a combination of administration of large volumes of magnesium-free fluids and binding with excess citrate from the stored blood products. Citrate binds to iMg2+ with the same affinity as it does to iCa2+, and this may lead to clinically important hypomagnesemia in patients receiving massive transfusions. Signs of hypomagnesemia tend to mimic those of hypocalcemia and include muscle spasm, CNS irritability, and cardiac arrhythmias. Treatment with magnesium chloride has been recommended for patients with hypomagnesemia following massive transfusion, as the sulfate ions in magnesium sulfate can bind to calcium and exacerbate a pre-existing hypocalcemia.

The prevalence of hyperkalemia in humans undergoing massive transfusion is reportedly low (10 to 12%). Hyperkalemia may develop in people after massive transfusion because K+ concentrations in stored human blood rise significantly over time as K+ is released from lysed RBC. Dogs are unique in having RBC lacking substantial concentrations of K+; therefore, hyperkalemia should not develop secondary to RBC lysis. For unknown reasons, Akitas and other dogs of Far East descent have K+ in their RBC, but such dogs are not routinely used as blood donors. Hyperkalemia was identified in 2 dogs in the present study in which K+ concentration after transfusion was measured, but these dogs also had severe acidosis or oliguria. Thus, the hyperkalemia was not clearly a direct effect of the transfusion. Serum concentrations of other electrolytes (Na+ and Cl–) did not change significantly in our dogs and have not been reported to be affected in humans undergoing massive transfusion.

Mild thrombocytopenia prior to transfusion was common among dogs in this study and was attributed to the underlying disease or injury. Progressive thrombocytopenia was a consistent finding following massive transfusion, with moderate thrombocytopenia (50 to 100 X 10^3/L) in all dogs for which post-transfusion platelet counts were available. These findings are comparable to those in human studies in which moderate thrombocytopenia was universal following administration of 15 units of blood (approx 50 ml/kg [23 ml/lb]). The mechanism by which thrombocytopenia develops following massive transfusion is multifactorial, although the primary cause in humans reportedly is dilution. Stored blood products become devoid of platelets after 2 days as a result of cell oxidation and death caused by the cold storage temperatures. Administering large volumes of platelet-free blood products, especially after administration of large volumes of crystalloid fluids, can result in a dilutional thrombocytopenia. However, the thrombocytopenia is generally less severe than would have been predicted on the basis of degree of dilution, because platelets are released from stores in the lungs and, possibly, the spleen. Blunt trauma, shock, sepsis, or systemic inflammation associated with the underlying illness or injury also trigger platelet consumption in patients receiving massive transfusions.

With massive transfusion and hemodilution, PT and APTT are progressively and simultaneously prolonged. As long as clotting factor concentrations are at least 30% of normal, corresponding to a PT and APTT < 150% of the control value, adequate hemostasis should be maintained. Marked elevations in PT and APTT (> 150% prolongation) were detected in 3 dogs, none of which survived. This suggests that in dogs, as in people, undergoing massive transfusion, severe coagulopathy may be considered a negative prognostic indicator. Because of the retrospective nature of this study, it was often difficult to determine the volumes of blood products and other fluids that had been administered prior to coagulation testing. It is likely that more coagulation abnormalities may have been detected if more dogs had been tested following administration of the entire transfusion volume.

A frequently reported complication of massive transfusion in humans is development of acid-base disturbances. Acid-base disturbances may be attributable to shock, the underlying disease process, or the transfusion itself. When RBC are stored for prolonged peri-
ods, glucose metabolism leads to an increase in concentrations of lactic and pyruvic acid. Thus, the pH of stored blood may be as low as 6.4 to 6.6, and severe acidosis may develop following massive transfusion.6 However, volume replacement and metabolism of citrate in stored blood products to bicarbonate may contribute to an improvement in acidosis following massive transfusion, as seen in 9 of 11 dogs in this study.

Hypothermia was detected in 9 of 13 dogs after massive transfusion in this study. In contrast, the reported prevalence of hypothermia in human studies is only 39%.3 In human intensive care units, the use of rapid blood infusers capable of warming large fluid volumes during infusion and the increased use of warm-air blankets have been reported to significantly decrease the prevalence of hypothermia.11 In our study, there was no apparent association between nadir rectal temperature and outcome, as 2 of 4 survivors had nadir rectal temperatures < 35.6 C (96 F). However, all but 3 dogs in the study underwent surgery, and the low temperatures may have been related to the surgery rather than to the transfusion itself. Because dogs are smaller than humans, the higher body surface area-to-weight ratio may also have contributed to more rapid cooling in these patients.

Transfusion reactions were documented in 6 of 15 patients in this study and consisted of febrile non-hemolytic reactions, delayed hemolysis, vomiting, and angioedema. Reactions were considered mild and self-limited in all cases. This is much higher than the prevalence of transfusion reactions in the general veterinary population, with published prevalences of approximately 3% at 2 veterinary institutions.3,38 While it might be appealing to attribute the apparently increased prevalence of reactions in the present study to the high number of units of blood products transfused, various human studies have not shown an increased prevalence of transfusion reactions following massive transfusion.7,8 It is possible that not all the reactions reported were true transfusion reactions. For example, hemolysis may have been related to microangiopathic hemolysis secondary to hemangiosarcoma or a result of mechanical lysis of donor cells during storage or administration.15 Closer scrutiny of the blood collection, storage, and administration practices may be required to identify a cause for the high prevalence of transfusion reactions in these dogs.

As might be expected, given the severity of illnesses and injuries that necessitate massive transfusion, a high mortality rate was identified (11/15). Previous reports7,8,12,13 in the human literature have identified mortality rates of between 40 and 75% following massive transfusion, with a variety of factors increasing the risk of death. The low number of survivors in the present study limited our ability to draw conclusions regarding relative risk factors.

Limitations to this study included the small population size, the missing data points for a number of dogs, and the retrospective nature of the study, which often made it difficult to determine the timing of testing in relation to timing of blood transfusion. This was particularly true for testing of coagulation parameters and electrolyte concentrations. Had data been available at regular intervals during and immediately after transfusion, analyses of the effects of transfused volumes on these variables could possibly have been performed.

Despite the expectation that injuries necessitating massive transfusion are likely to be associated with a poor outcome, this study demonstrates that patients with such injuries can be successfully managed. Because abnormalities in electrolyte concentrations were so commonly identified, we recommend that patients receiving massive transfusions of blood products be monitored for changes in iCa2+ concentration, particularly if hypotension or arrhythmias are detected. Point-of-care testing has proven to be a useful tool in these patients, as samples sent to a laboratory rarely are able to provide timely information on these values. Rapid identification and treatment of coagulation abnormalities appears important to the successful management of patients receiving massive transfusion, so performing coagulation testing both before and after massive transfusion should be considered. Transfusion of FFP should be considered for patients with prolongation of PT or APTT consistent with coagulopathy. Because hypothermia is common in patients undergoing massive transfusion and has been associated with development of microvascular bleeding,22 careful attention should be paid to rewarming when managing these patients.

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